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Indicadores Antropométricos Precoces e Medidas de Adiposidade, Biomarcadores Cardiometabólicos, Aptidão Cardiorrespiratória e Atividade Física em Adolescentes

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Palavras-chave: PESO AO NASCER, ADIPOSIDADE, MARCADORES CARDIOMETABÓLICOS, APTIDÃO CARDIORRESPIRATÓRIA, ATIVIDADE FÍSICA, ADOLESCENTES

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A Viagem

Aparelhei o barco da ilusão
E reforcei a fé de marinheiro.
Era longe o meu sonho, e traiçoeiro
O mar...
(Só nos é concedida
Esta vida
Que temos;
E é nela que é preciso
Procurar
O velho paraíso
Que perdemos).
Prestes, larguei a vela
E disse adeus ao cais, à paz tolhida.
Desmedida,
A revolta imensidão
Transforma dia a dia a embarcação
Numa errante e alada sepultura...
Mas corto as ondas sem desanimar.
Em qualquer aventura,
O que importa é partir, não é chegar.

Miguel Torga, *in* Câmara Ardente, 1962

À memória de minha Mãe

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Resumo

Indicadores antropométricos tão precoces como o peso ao nascer e o índice de massa corporal (IMC) durante os primeiros anos de vida são tidos como determinantes relevantes no desenvolvimento de parâmetros de saúde importantes em períodos futuros.

A presente tese teve assim quatro objetivos principais interrelacionados e sequenciais. O primeiro objetivo consistiu em determinar se os indicadores antropométricos estudados desde o nascimento até aos 6 anos de idade, possuem capacidade discriminatória de previsão de níveis aumentados de adiposidade na adolescência (Artigo I); o segundo objectivo pretendeu verificar se, e quais as medidas de adiposidade que possuem capacidade discriminatória na previsão de níveis aumentados de biomarcadores inflamatórios e metabólicos, em adolescentes (Artigo II); o terceiro objetivo procurou explorar as associações entre indicadores antropométricos do nascimento aos 6 anos de idade e biomarcadores inflamatórios, resistência à insulina e perfil lipídico na adolescência (Artigo III); o quarto objectivo estudou as associações entre os indicadores antropométricos do nascimento até aos 6 anos de idade e a aptidão cardiorrespiratória, a atividade física e o tempo sedentário na adolescência (Artigo IV).

Considerando os nossos objetivos iniciais e as estratégias delineadas para alcançá-los, os resultados obtidos nos estudos originais parecem razoáveis para suportar as seguintes conclusões:

Desde idades muito precoces, o IMC apresentou capacidade discriminatória para classificar corretamente adolescentes numa categoria desfavorável de IMC, percentagem de massa gorda, perímetro de cintura ou rácio cintura-estatura, em ambos os sexos; essas medidas de adiposidade geral e abdominal apresentaram capacidade para detectar níveis aumentados de alguns biomarcadores inflamatórios e metabólicos em adolescentes, mas nenhuma das medidas de adiposidade prevaleceu sobre as outras.

Um IMC desfavorável a partir dos 2 anos de idade foi consistentemente associado a piores perfis inflamatórios e a um aumento da resistência à insulina na adolescência; e, a partir dos 5 anos, a um rácio colesterol total/HDL mais elevado; O IMC durante os primeiros anos de vida apresentou também associações negativas consistentes com a aptidão cardiorrespiratória na adolescência, para ambos os sexos. Em relação à atividade física, os resultados obtidos foram mistos, com ausência de associações nas meninas, e associações positivas entre o IMC aos 3, 5 e 6 anos e atividade física moderada e moderada-a-vigorosa na adolescência, nos rapazes.

O peso ao nascer não foi um bom preditor de excesso de peso na adolescência, independentemente da medida de adiposidade utilizada para identificar essa condição. Para além disso, o peso ao nascer não apresentou associações com a aptidão cardiorrespiratória, atividade física ou tempo sedentário, nem com qualquer indicador cardiometabólico na adolescência.

Os nossos resultados suportam as recomendações para uma monitorização regular do IMC desde cedo, para a detecção de uma condição de excesso de peso e uma consequente intervenção, que vise prevenir ou reverter essa condição durante a infância, na tentativa de contribuir para melhorar uma série de parâmetros de saúde importantes que a ela se associam durante a adolescência, que vão além da adiposidade excessiva em si mesma.

Palavras-chave: PESO AO NASCER, ADIPOSIDADE, BIOMARCADORES CARDIOMETABÓLICOS, APTIDÃO CARDIORRESPIRATÓRIA, ATIVIDADE FÍSICA, ADOLESCENTES

Abstract

Early anthropometric indicators such as birth weight and body mass index (BMI), during the first years of life, are considered relevant determinants for the development of important health parameters in future periods.

The present thesis had four interrelated and sequential main aims. The first one was to determine if the anthropometric indicators from birth to 6 years of age have discriminatory ability in identifying increased levels of adiposity in adolescence (Paper I). The second objective was to verify if, and which of the adiposity measures had discriminatory ability in diagnosing increased levels of inflammatory and metabolic biomarkers in adolescents (Paper II). The third objective explored the associations of anthropometric indicators from birth to 6 years of age with inflammatory biomarkers, insulin resistance and lipid profile in adolescence (Paper III). The fourth objective studied the associations between anthropometric indicators from birth to 6 years of age with cardiorespiratory fitness, physical activity and sedentary time in adolescence (Paper IV).

Considering our initial aims and the strategies outlined to achieve them, the results obtained in the original studies seem reasonable to support the following conclusions:

From a very young age, BMI presented discriminatory ability to correctly classify adolescents as belonging to an unfavourable BMI category, body fat percentage, waist circumference or waist-to-height ratio, in both sexes; these measures of overall and abdominal adiposity were able to detect increased levels of some inflammatory and metabolic biomarkers in adolescents, but none of the adiposity measures prevailed over the others.

An unfavourable BMI from 2 years of age onwards was consistently associated with worse inflammatory profiles and increased insulin resistance in adolescence, and from 5 years, with a higher total cholesterol/HDL ratio. BMI during the first years of life also showed consistent negative associations with cardiorespiratory fitness in adolescence for both sexes. Regarding physical activity, the results were mixed, with no associations for girls, and positive associations between BMI at 3, 5 and 6 years and moderate and moderate-to-vigorous physical activity in adolescence, for boys.

Birth weight was not a good predictor of overweight in adolescence, regardless of the adiposity measure used to identify this condition. In addition, birth weight did not show associations with cardiorespiratory fitness, physical activity or sedentary time, or with any cardiometabolic indicator, in adolescence.

Our results support the recommendations for a regular monitoring of BMI from an early age, for the detection of excess weight and consequent intervention for preventing or reversing this condition during childhood, in an attempt to improve a series of health parameters associated with it during adolescence.

Keywords: BIRTH WEIGHT, ADIPOSITY, CARDIOMETABOLIC BIOMARKERS, CARDIORESPIRATORY FITNESS, PHYSICAL ACTIVITY, ADOLESCENTS

Lista de Abreviaturas

AUC: Area under the curve

BF%: Body fat percentage

BMI: Body mass index

BW: Birth weight

C3: Complement factor C3

C4: Complement factor C4

CI: Confidence interval

CIAFEL: Centro de Investigação em Atividade Física, Saúde e Lazer

cpm: Counts per minute

CRF: Cardiorespiratory fitness

CRP: High sensitivity C-reactive protein

CT: Colesterol total

CT/HDL: Rácio colesterol total/lipoproteínas de alta densidade

DEXA: Absorciometria radiológica de dupla energia

ESR: Erythrocyte sedimentation rate

FAS: Family Affluence Scale

HDL: Lipoproteínas de Alta Densidade

HOMA-IR: Homeostatic Model Assessment of Insulin Resistance

IL-6: Interleukin-6

IMC: Índice de Massa Corporal

LabMed Physical Activity Study: Longitudinal Analysis of Biomarkers and Environmental Determinants of Physical Activity Study

LDL: Lipoproteínas de baixa densidade

LPA: Light Intensity physical activity

MET: Metabolic Equivalent Task/ Equivalente metabólico

MPA: Moderate intensity physical activity

MVPA: Moderate-to-vigorous intensity physical activity

n.s.: Non-significant

NW: Normal weight

OB: Obese

OW: Overweight

PA: Physical activity

PCR: Proteína C-reativa de alta sensibilidade

ROC: Receiver Operating Characteristic

SD: Standard Deviations

SED time: Sedentary time

SPSS: Statistical Package for Social Sciences

TC: Total cholesterol

TC/HDL: Total cholesterol to high density lipoproteins ratio

UW: Underweight

VO_2max: Consumo máximo de oxigénio

VPA: Vigorous intensity physical activity

WBC: White blood cells

WC: Waist circumference

WHR: Waist-to-hip ratio

WHtR: Waist-to-height ratio

WsHtR: Waist-to-sitting-height ratio

Estrutura da Tese

A presente tese está organizada em seis capítulos.

O Capítulo I faz a introdução e o enquadramento teórico dos temas e problemas em questão que levaram à realização da presente tese, através de uma revisão da literatura mais relevante acerca das temáticas abordadas.

Os principais objetivos da tese e uma apresentação sumária de cada artigo original são delineados no Capítulo II.

O Capítulo III apresenta uma visão geral e resumida dos métodos utilizados na recolha das variáveis utilizadas nos artigos originais.

No Capitulo IV são apresentados os quatro artigos originais realizados.

A discussão geral, abrangendo e analisando os resultados globais obtidos nos artigos, bem como as principais conclusões desta tese, são apresentadas no Capítulo V.

O Capitulo VI indica as referências bibliográficas que serviram de suporte à elaboração da tese.

CAPÍTULO I

INTRODUÇÃO E ENQUADRAMENTO TEÓRICO

Introdução e Enquadramento Teórico

O peso ao nascer representa uma medida antropométrica que historicamente tem sido alvo de atenção (Brisbois et al., 2012; Hughes et al., 2017; Wells, 2009), provavelmente por representar a primeira ocasião onde um indivíduo pode ser avaliado objetivamente. Uma vez que mesmo em contextos socioeconómicos considerados mais desfavoráveis o acesso ao seu registo é feito com relativa facilidade, comparativamente a outras variáveis dos períodos pré e perinatal, o peso ao nascer tem sido usado, desde há muito tempo, como uma medida indicativa (*proxy)* do desenvolvimento intrauterino em vários estudos (Barker, 1995; Eriksson et al., 2001a; Hemachandra et al., 2007; McDade et al., 2014; Oglund et al., 2015; Sacco et al., 2013; van Deutekom et al., 2013).

A Organização Mundial de Saúde define baixo peso ao nascer como sendo um valor inferior a 2500 g, independentemente do tempo de gestação (WHO & UNICEF, 2004). A definição deste ponto de corte é sustentada em observações decorrentes de estudos epidemiológicos, onde se concluiu que bebés com peso ao nascer inferior a 2500g apresentavam uma probabilidade aproximadamente 20 vezes maior de morrer, do que bebés com um peso superior a esse valor (Kramer, 1987). Este valor tem sido amplamente acolhido pela comunidade científica (Hughes et al., 2017). Já para o peso elevado ao nascer, ou macrossomia, não existe um valor unanimemente aceite (Walsh & McAuliffe, 2012), pois apesar da grande maioria dos estudos o considerarem como sendo um valor superior a 4000 g (Andersen et al., 2012; Bekkers et al., 2011; Cunningham et al., 2014; Labayen et al., 2013; Rugholm et al., 2005), valor este que também tem sido referido em revisões sistemáticas e meta-análises (Harder et al., 2007; Schellong et al., 2012; Yu et al., 2011), outros definem-no como valor mínimo de 4500 g (Evensen et al., 2017; van Dijk & Innis, 2009) ou até mesmo 5000g (Walsh & McAuliffe, 2012).

O baixo peso ao nascer é geralmente entendido como sendo consequência de um parto pré-termo (considera-se um parto de termo quando

este acontece entre as 37 e as 42 semanas de gestação), ou devido a problemas ou perturbações durante o desenvolvimento fetal, ou ainda a uma combinação de ambos, e por isso é visto como um indicador importante de mortalidade e morbilidade fetal e neonatal (WHO & UNICEF, 2004).

Durante os anos 80, David Barker surgiu como o primeiro proponente da *Teoria da Origem Fetal das Doenças do Adulto (Fetal Origins of Adult Disease)*. A “Hipótese de Barker" é uma hipótese genérica de associações entre um baixo peso ao nascer e a ocorrência de doenças cardiovasculares em idades mais avançadas (Barker, 1995; Barker et al., 1993a; Barker & Osmond, 1986). Em 1989 surgiu a primeira de uma série de publicações provenientes de um estudo de coorte de homens nascidos em Hertfordshire, durante as décadas de 1910 e 1920, que sugeriram que as doenças cardiovasculares (particularmente doenças isquémicas) estavam inversamente associadas ao peso ao nascer (Barker et al., 1989; Osmond et al., 1993), e desde então, o peso ao nascer tem sido explorado como um determinante precoce de outras patologias em períodos futuros da vida, tais como diabetes tipo 2 e síndrome metabólica (Chen et al., 2012; Johnsson et al., 2015; Vaag, 2009), bem como de outros parâmetros relacionados com a saúde, como por exemplo a composição corporal (Barker, 2007; Rugholm et al., 2005; Ye et al., 2010).

Na sequência das investigações de Barker e colaboradores surge a *Hipótese do Fenótipo Poupador* (*The Thrifty Phenotype Hypothesis*) (Hales & Barker, 1992), que postula que quando o ambiente intrauterino é nutricionalmente pobre, o feto sofre um processo de programação onde se prioriza a proteção do desenvolvimento de alguns órgãos vitais e que se este processo for seguido de uma melhoria na disponibilidade nutricional durante a primeira infância, provoca um aumento do risco de futuros distúrbios metabólicos. Esta hipótese supõe que o crescimento fetal retardado pode resultar num número reduzido de células β, alterando a funcionalidade do pâncreas e resultando numa redução da sensibilidade à insulina e aumento da resistência à mesma (Barker, 1997; Ravelli et al., 1998).

Para além dos anteriores, entroncam também nesta perspectiva uma

série de trabalhos tendo por base o *Helsinki Birth Cohort Study* (Barker et al., 2005; Barker et al., 2009), constituído por um grupo de homens e mulheres nascidos no Hospital Central da Universidade de Helsínquia, divididos em duas coortes, uma mais antiga com indivíduos nascidos entre 1924-1933, e outra mais jovem, com indivíduos nascidos entre 1934-1944, com dados sobre o peso e comprimento ao nascer e medidas de peso e estatura durante os anos escolares. Também num outro estudo longitudinal, composto por 14611 crianças nascidas entre 1915 e 1929 no Hospital Universitário de Uppsala na Suécia, Leon et al. (1998) verificaram associações inversas entre o crescimento fetal e mortalidade por doença cardíaca isquémica.

É reconhecido que os períodos de fome tiveram efeitos profundos na saúde global das populações (Painter et al., 2005). Por exemplo, durante o período da *Fome Holandes*a nos finais de 1944 devido à 2ª Grande Guerra Mundial, a taxa de mortalidade em Amesterdão em 1945 era mais do dobro do que em 1939, e pensa-se que grande parte deste aumento terá sido devido precisamente a problemas nutricionais (Banning, 1946). Cumulativamente, os efeitos negativos que a desnutrição materna em diferentes períodos de gestação dos bebés que foram concebidos nesse período possam ter tido na saúde destes, já durante as suas vidas adultas, puderam ser posteriormente estudados nesta população sujeita a estas circunstâncias (Painter et al., 2005; Ravelli et al., 1998; Roseboom et al., 2011; Roseboom et al., 2001). Porém, também foi verificado que, embora a exposição à fome nos períodos médios e finais de gestação se associasse com um menor peso e comprimento ao nascer, não se verificaram diferenças no índice de massa corporal (IMC) ou no perímetro de cintura desses mesmos indivíduos aos 50 anos de idade (Ravelli et al., 1999).

No entanto, deve ser levado em conta que o conceito de programação fetal e as eventuais consequências patofisiológicas que daí pudessem advir, provêm dos estudos pioneiros de Barker et al. (1989) e Hales et al. (1991), que foram conduzidos em populações nascidas nas primeiras décadas do século passado, que nasceram e cresceram num ambiente pré 2ª Grande Guerra Mundial, mas que atingiram a sua maturação e foram avaliados relativamente a

parâmetros de saúde num outro período. Ou seja, todos os estudos referidos anteriormente têm como característica comum serem de períodos temporais com condições sociodemográficas muito diferentes das atuais, e isso pode representar uma das razões para uma eventual relativização da importância atribuída atualmente ao peso ao nascer no desenvolvimento de doenças cardiometabólicas em coortes mais contemporâneas (Jeffery et al., 2006; Leunissen et al., 2009a). A taxa de mortalidade infantil tem vindo a diminuir consideravelmente a nível mundial desde o período pós-guerra (Wilcox, 2001), principalmente nos países desenvolvidos (WHO, 2017), e, concomitantemente, em certas partes da Europa, Estados Unidos da América e Canadá tem-se verificado em períodos mais recentes uma maior proporção de bebés nascidos com peso elevado ao nascer (Ananth & Wen, 2002; Kramer et al., 2002; Surkan et al., 2004). Para além disso, um peso ao nascer elevado (nestes casos tendo como referência valores superiores a 4000g) tem sido associado de forma mais consistente a um maior risco futuro de excesso de peso/obesidade em amostras de faixas etárias distintas, seja em estudos com meninas e meninos com idades de 4-5 anos (Oldroyd et al., 2011), entre os 9-11 anos (Qiao et al., 2015), com crianças e adolescentes na faixa etária dos 6 aos 13 anos (Rugholm et al., 2005), ou em jovens adultos (Johnsson et al., 2015; Skilton et al., 2014).

No entanto, a literatura tem demonstrado resultados inconsistentes, e, como tal, existem atualmente diferentes posições acerca de se, e como, o peso ao nascer pode de facto influenciar o risco de excesso de peso/obesidade em idades adultas ou pediátricas, bem como outros parâmetros relacionados com a saúde. Alguns estudos propõem curvas de associação em forma de J (Hui et al., 2008; Parsons et al., 2001; Schellong et al., 2012; Woo Baidal et al., 2016; Ye et al., 2010) e de U (Baker et al., 2008; Dubois & Girard, 2006; Qiao et al., 2015), mas também ausência de associações (Boreham et al., 2001; Brisbois et al., 2012; Rugholm et al., 2005; Yu et al., 2011). Para além das relações estudadas maioritariamente com o peso corporal ou com o IMC, outros trabalhos também procuraram investigar se, e de que forma, o peso ao nascer se associa com outras medidas de adiposidade em crianças e adolescentes,

tais como o perímetro de cintura e a percentagem de massa gorda (Ridgway et al., 2011a; Rogers et al., 2006; Sacco et al., 2013).

A avaliação da composição corporal pode ser realizada através de métodos laboratoriais, ou por alguns métodos de terreno. Os métodos laboratoriais, considerados *gold standard*, incluem técnicas densitométricas como a hidrodensitometria (ou pesagem hidrostática) ou a pletismografia por deslocamento de ar, bem como técnicas radiológicas tais como a absorciometria radiológica de dupla energia (DEXA), tomografia axial computadorizada ou ressonância magnética (Wells & Fewtrell, 2006). No entanto, devido aos custos elevados associados a esses equipamentos e aos técnicos especializados no seu manuseamento, restrições de tempo e mobilização da amostra, a adiposidade excessiva também pode ser estimada através de vários métodos de terreno. Estes incluem uma série de técnicas antropométricas abrangendo medições de pesos, comprimentos, perímetros, pregas de adiposidade subcutânea e índices combinados destas medidas, bem como a bioimpedância, e são normalmente utilizados em estudos epidemiológicos para estimar a percentagem de massa gorda de um indivíduo (Cornier et al., 2011) ou classificar os sujeitos relativamente ao seu estatuto ponderal ou de adiposidade, como alternativas para uma avaliação laboratorial mais precisa, mas dificilmente viável no contexto dos estudos de campo com grandes amostras (Li et al., 2006).

O método das pregas de adiposidade subcutânea baseia-se no conceito de que a medição de tecido adiposo subcutâneo em determinadas localizações anatómicas especificas, pode fornecer uma boa estimativa da percentagem de gordura corporal total (Deurenberg et al., 1990; Rodriguez et al., 2011), obtida através da utilização de equações de regressão, como por exemplo as de Slaughter et al. (1988). Embora esta metodologia seja bastante simples na sua essência (Lohman et al., 1988), e tem sido amplamente utilizada para a medição de gordura corporal em contextos epidemiológicos (Cornier et al., 2011), tem como limitação principal requerer avaliadores experientes que dominem todos os requisitos relacionados com os procedimentos de medição, para minimizar erros de medida.

A bioimpedância elétrica também é considerada um método prático para estimar a percentagem de massa gorda em adolescentes em contextos epidemiológicos (McCarthy et al., 2006), desde que num ambiente controlado e em grupos da mesma etnia, e sem qualquer condição médica (Bohm & Heitmann, 2013; Dehghan & Merchant, 2008). É considerado um método simples (não é necessário nenhum treino especial dos avaliadores), rápido, económico, indolor e não invasivo. Esta técnica mede a impedância do corpo a uma corrente elétrica de baixa intensidade, que chega ao corpo através de dois eléctrodos "emissores" e que é recebida pelos eléctrodos "receptores", e, de uma forma simplificada, baseia-se na premissa de que o tecido magro atua como um bom condutor do impulso elétrico, enquanto a gordura resiste a essa transmissão. Como tal, requer a observância de uma série de pressupostos relacionados com o equilíbrio hídrico dos sujeitos, tais como não ter ingerido alimentos líquidos nem sólidos há pelo menos 4 horas, ou consumido álcool há pelo menos 48 horas, não ter efectuado atividade física intensa há pelo menos 12 horas, e especificamente para o sexo feminino, não estar grávida ou no período menstrual.

Para definir e caracterizar uma condição de adiposidade excessiva, diferentes terminologias têm vindo a ser utilizadas indiferenciadamente, e os termos excesso de peso e obesidade têm sido usados comummente para referir massa gorda em excesso, independentemente das medidas de adiposidade utilizadas. No entanto, o peso não é sinónimo de gordura, uma vez que a densidade do tecido muscular esquelético dos mamíferos (1,06 g/cm$^{3)}$ (Mendez, 1960) é superior à densidade do tecido adiposo (0,92 g/cm^3) (Farvid et al., 2005). Além disso, o peso corporal por si só tem pouco significado, caso não seja relativizado pela estatura do sujeito.

Sendo uma razão do peso corporal pela estatura ao quadrado, o IMC classifica um indivíduo numa categoria ponderal que pode ser abaixo do peso normal, peso normal, excesso de peso ou obeso, de acordo com pontos de corte estabelecidos, que para adultos são independentes do sexo e da idade, mas que no caso de crianças e adolescentes levam em consideração estas duas variáveis (Cole et al., 2000; WHO, 2007). Uma das maiores reservas em

relação à utilização do IMC é a sua incapacidade de fornecer informação objectiva relativamente à composição corporal do sujeito, nomeadamente distinguir entre massa isenta de gordura e massa gorda, bem como as suas distribuições corporais (Freedman et al., 2005). Porém, também se reconhece que um valor elevado de IMC ajustado à idade é um bom indicador de massa gorda em excesso (Dietz & Bellizzi, 1999; Freedman & Sherry, 2009), e apesar das suas limitações, mas devido à sua simplicidade, o IMC continua provavelmente a ser o método mais utilizado para avaliar o estatuto ponderal e para identificar uma situação de excesso de peso/obesidade (Afshin et al., 2017; Cole et al., 2000; WHO, 2000), bem como para fazer a sua monitorização, uma vez que esta condição parece manter-se desde idades jovens até à adolescência e idade adulta (de Kroon et al., 2011; Evensen et al., 2016; The et al., 2010). Para além disso, o IMC parece ser preditivo de uma série de parâmetros clínicos em adultos, como por exemplo doenças cardiovasculares e diabetes tipo 2, embora em crianças e adolescentes esse poder preditivo pareça ser menos claro (Twig et al., 2016; Wells & Fewtrell, 2006).

A percentagem de massa gorda corporal representa a gordura corporal total expressa em percentagem do peso corporal total, e, tal como para o IMC, os valores que definem a normalidade ou excesso de adiposidade em crianças e adolescente são dependentes do sexo e da idade. O estudo de McCarthy et al. (2006), que avaliou a massa gorda de crianças e adolescentes Britânicos entre os 5 e os 18,5 anos de idade, recorrendo ao método de bioimpedância, propôs curvas de referência para a percentagem de massa gorda nessa faixa etária, definindo como pontos de corte o percentil 2 para uma categoria de *underfat,* ou seja, abaixo da gordura corporal considerada saudável*,* acima do percentil 85 para definir *overfat* (correspondente ao excesso de peso no IMC), e obesidade acima do percentil 95.

Outras medidas de adiposidade, como o perímetro de cintura, e rácios calculados a partir desta medida, como por exemplo o rácio cintura/estatura, rácio cintura/anca e rácio cintura/estatura sentado, focam especificamente a obesidade abdominal, apesar de não conseguirem distinguir as componentes

visceral, retroperitoneal e subcutânea, são reconhecidas como um factor de risco independente para a resistência à insulina e doenças cardiovasculares em crianças e adolescentes (Berg & Scherer, 2005; Freedman et al., 1999; Li et al., 2006).

De um modo geral, as associações que foram sendo descritas na literatura entre os determinantes precoces e uma série de parâmetros relacionados com a saúde, colocaram uma grande ênfase no peso ao nascer como um marco epidemiológico em si mesmo. No entanto, alguns autores (Jeffery et al., 2006; Lucas et al., 1999; Wilcox, 2001) sugerem que essa ênfase é excessiva, por considerarem que o peso ao nascer oferece pouca informação acerca da saúde futura da população. Como tal, alguns estudos (Baker et al., 2007; Demerath et al., 2009; Leunissen et al., 2009a; Leunissen et al., 2009b; Monteiro et al., 2003; Rolfe et al., 2010) têm vindo a sugerir que, mais do que o peso ao nascer *per se,* poderão ser os padrões de crescimento durante a infância a ter um efeito mais pronunciado na programação da composição corporal, ou numa condição de excesso de peso/obesidade em períodos futuros.

Tome-se como exemplo os estudos de Parsons et al. (2001), onde foi verificado que, em rapazes que cresceram de forma rápida, o risco de se tornarem obesos na idade adulta era semelhante, quer tenham nascido com baixo peso ou com peso elevado, e também de Ekelund et al. (2006), que reportaram que ganhos de peso entre os 3 e os 6 anos de idade não se associaram significativamente com o peso ao nascer, mas sim com uma maior quantidade de massa gorda, perímetro de cintura e IMC aos 17 anos de idade.

Outros estudos com crianças demonstraram que um ganho rápido de peso durante os primeiros doze meses de vida (Hui et al., 2008) e o IMC no primeiro ano de idade (Peneau et al., 2011) se associavam positivamente a um maior IMC e maior risco de excesso de peso entre os 7 e os 9 anos de idade. Botton et al. (2008) verificaram num estudo longitudinal que o peso ao nascer não se associou mais tarde com o IMC nem com a massa gorda de adolescentes de ambos os sexos, enquanto que o ganho rápido de peso aos 3

e 5 anos se correlacionou positivamente com o IMC, perímetro de cintura, soma de pregas de adiposidade subcutânea e com a quantidade de massa gorda durante a adolescência.

Alguns autores (Gardner et al., 2009; Pei et al., 2013) indicam que o período de tempo em torno dos 5/6 anos de idade, coincidente com o início do percurso escolar (Mattocks et al., 2008) e que implica uma série de mudanças de rotinas na vida das crianças, é uma fase crítica para o desenvolvimento do excesso de peso e de obesidade, bem como de complicações associadas a essas condições. Num estudo longitudinal de 9 anos, Gardner et al. (2009) relataram que o peso aos 5 anos de idade apresentou pouca relação com o peso ao nascer, mas que se revelou um preditor fiável do peso aos 9 anos de idade. Outros estudos indicaram que crianças com excesso de peso aos 5 anos apresentam uma probabilidade 10 vezes maior de manterem essa condição aos 10 anos de idade (Pei et al., 2013), e que crianças com excesso de peso aos 6 e 9 anos de idade tinham uma probabilidade de 10,4 e 18,6 vezes, respetivamente, de terem excesso de peso aos 15 anos, em comparação com os seus pares normoponderais (Johannsson et al., 2006).

Estudos que focaram especificamente a obesidade abdominal verificaram que crianças com um crescimento acelerado entre o nascimento e os dois anos de idade, apresentaram uma maior distribuição de gordura central aos 5 anos (Ong et al., 2000), e que um aumento precoce de peso nos primeiros 18 meses de vida estava associado a maior adiposidade abdominal aos 8 anos de idade (Skilton et al., 2013). Mesmo em estudos com adultos, foram reportadas ausências de associações entre o peso ao nascer e o perímetro de cintura (Rolfe et al., 2010), e outros autores consideraram que, mais do que o peso ao nascer, foi o aumento rápido de peso durante a infância que se associou a uma maior obesidade abdominal, bem como à adiposidade total na idade adulta (Araújo de França et al., 2016; Demerath et al., 2009).

Importa realçar que as associações entre o peso ao nascer e os níveis

de adiposidade em períodos futuros são complexas de explicar, uma vez que é muito difícil distinguir a influência do peso ao nascer da do crescimento pós-natal, bem como definir qual é o determinante mais importante na evolução a longo prazo de parâmetros associados à saúde e isso é uma preocupação partilhada por vários autores (Eriksson et al., 2001a; Leunissen et al., 2009b; Lucas et al., 1999). Para além disso, algumas questões relativamente à validade das associações entre o peso ao nascer e alguns parâmetros relacionados com a saúde na vida adulta têm sido levantadas (Huxley et al., 2002; Lucas et al., 1999), uma vez que essas associações podem ser devidas, em parte, a um ajuste estatístico inapropriado para algumas variáveis, criando assim um artefacto estatístico (Tu et al., 2005).

Pela análise da literatura parece verificar-se a existência de duas perspectivas teóricas subjacentes aos estudos que avaliam o papel dos indicadores antropométricos precoces e os seus efeitos numa eventual condição de excesso de adiposidade no futuro. Uma delas de enfoque mais biológico, relacionada com a hipótese de programação fetal suportada na teoria inicial de Barker; e uma outra que inclui fatores pós-natais para o risco de obesidade futura, tais como os ganhos rápidos de peso durante a infância, ou a velocidade do crescimento através do cruzamento de percentis, que representa no fundo a evolução das teorias iniciais de Barker e Halles em direção à atualmente denominada *Developmental Origin of Health and Disease* (Gillman, 2005). Para além disso, parecem existir diferenças nos resultados de coortes mais contemporâneas, comparativamente com coortes mais antigas, que se basearam em registos históricos de crescimento durante os anos de guerra mundial e pós-guerra (Barker et al., 2005; Eriksson et al., 2006), podendo refletir tendências seculares de aumentos do excesso de peso e obesidade na infância que se verificam atualmente.

O excesso de peso e a obesidade são considerados fatores de risco importantes no desenvolvimento de uma série de doenças cardiometabólicas (Heymsfield & Wadden, 2017), que embora na maioria das vezes permaneçam latentes e assintomáticas durante grande parte da juventude, e apenas se manifestem na idade adulta, podem ter a sua origem durante a infância (Berenson et al., 1998; Juonala et al., 2011; Twig et al., 2016).

Atualmente o tecido adiposo não é mais reconhecido como sendo apenas um armazenamento de massa gorda, mas sim como um órgão endócrino e uma importante fonte secretora de hormonas e citoquinas com ação local e/ou sistémica (Adamczak & Wiecek, 2013). Porém, a facilidade que o tecido adiposo apresenta em desenvolver-se excessivamente, pode conduzir a uma série de alterações a nível molecular e celular que podem afectar o normal equilíbrio do metabolismo sistémico (Greenberg & Obin, 2006; Weiss & Caprio, 2005).

Uma série de indicadores antropométricos como o IMC (Ford et al., 2001), bem como outros mais específicos da obesidade abdominal, tais como o perímetro de cintura (Steene-Johannessen et al., 2010), rácio cintura/anca (El-Wakkad et al., 2013) e rácio cintura/estatura (Khoury et al., 2013), têm vindo a demonstrar associações consistentes com vários biomarcadores de inflamação sistémica de baixo grau em jovens. Embora a proteína C-reativa (PCR) seja considerada o biomarcador inflamatório mais comum, outros reagentes de fase aguda tais como o fibrinogénio e factores de complemento C3 e C4 , citocinas como a interleucina-6, adipocinas como a leptina e a adiponectina, e biomarcadores não-específicos de inflamação sistémica tais como a velocidade de sedimentação e os leucócitos, têm vindo a ser explorados no sentido de avaliar o risco de doenças cardiovasculares e caracterizar mais detalhadamente o perfil inflamatório de um indivíduo (Balagopal et al., 2011; Calder et al., 2013; Calderon & Wener, 2012; Hertle et al., 2014; Hertle et al., 2012; Pearson et al., 2003), não apenas na população adulta, mas mostrando-se válidos também em estudos com crianças e adolescentes (Artero et al., 2014; Cohen et al., 2012; Guran et al., 2007; Labayen et al., 2009; Martinez-Gomez et al., 2011).

Embora a monitorização de rotina de biomarcadores não esteja preconizada em idades precoces, Skinner et al. (2010) mostraram que, em crianças tão novas quanto a idade de 3 anos, vários biomarcadores inflamatórios apresentam já uma forte associação positiva com o excesso de peso. Também Skilton et al. (2013) reportaram uma associação entre o aumento precoce de peso nos primeiros 18 meses de vida e níveis indicativos de inflamação sistémica de baixo grau em crianças com apenas 8 anos de idade.

As evidências decorrentes de estudos transversais nesta área vão no sentido de que, quanto mais cedo se dá o desenvolvimento da adiposidade excessiva e suas circunstâncias, e quanto mais tempo um individuo mantiver uma condição de excesso de peso durante a adolescência e a idade adulta, mais adversos serão os seus níveis de adipocinas e biomarcadores inflamatórios em períodos posteriores da vida (Murray et al., 2015), e maior parece ser o risco do início precoce de uma série de distúrbios cardiometabólicos (D'Adamo & Caprio, 2011; DeBoer, 2013). Apesar da sugestão de que o estado pró-inflamatório apresenta uma tendência para se manter desde a adolescência (e eventualmente desde a infância) até à idade adulta (Juonala et al., 2006; Pirkola et al., 2010; Wen et al., 2014), pouco se conhece ainda acerca de eventuais períodos sensíveis durante a infância que possam afectar um posterior risco metabólico (Bornhorst et al., 2016).

Como tal, uma atribuição puramente causal do desenvolvimento fetal na programação de doenças cardiovasculares em períodos mais avançados da vida não está ainda comprovada (Singhal & Lucas, 2004). De facto, vários estudos com crianças e adolescentes (Cook et al., 2000; Gillum, 2003; Labayen et al., 2009; Rondó et al., 2013) não conseguiram encontrar uma associação significativa entre o peso ao nascer e os níveis atuais de PCR. Apesar de menos frequentes na literatura, associações com outros biomarcadores inflamatórios, para além da PCR, têm sido exploradas. Também não foram encontradas associações entre o desenvolvimento fetal e os níveis de fibrinogénio em crianças com 10 e 11 anos de idade (Cook et al., 1999) e

em adultos (Barker et al., 1992), nem com os níveis de adiponectina de adolescentes com idades entre os 12 e 15 anos (Kim et al., 2006).

Contrariamente ao estudo de Cook et al. (1999), Labayen et al. (2009) verificaram que o peso ao nascer se associava negativamente com o fibrinogénio, bem como com outros biomarcadores inflamatórios, tais como os factores de complemento C3 e C4, e leptina (Labayen et al., 2011). Um outro estudo, com crianças e adolescentes com idades compreendidas entre os 4 e os 17 anos de idade, também mostrou uma associação inversa entre o peso ao nascer e os níveis de leucócitos (Chen et al., 2009). No entanto, importa igualmente referir que todos estes estudos utilizaram não só amostras compostas por sujeitos com idades diferentes, como também ajustes a variáveis de confusão distintas, e por isso estes resultados devem ser analisados levando este facto em consideração.

Rondó et al. (2013) sugerem que o tempo pode ser um factor importante para as alterações metabólicas associadas às concentrações de PCR, que parecem ir aumentando desde a infância até a idade adulta. De facto, alguns estudos com adultos têm indicado associações entre o peso ao nascer e os níveis de PCR. Neste sentido, os trabalhos de McDade e colaboradores sugerem que o baixo peso ao nascer foi um preditor significativo dos níveis de PCR aos 21 anos de idade (McDade et al., 2010), bem como entre os 24–32 anos (McDade et al., 2014). A mesma conclusão é retirada de outros estudos com adultos mais velhos, onde se verificou que o baixo peso ao nascer contribuiu para a elevação dos níveis de PCR aos 31 anos de idade (Tzoulaki et al., 2008), e noutra amostra de sujeitos com idades compreendidas entre os 30 e os 59 anos (Sattar et al., 2004).

No entanto, também são reportados dados contraditórios. Um estudo longitudinal, com 137 indivíduos afro-americanos com idades a rondar os 30 anos de idade, indicou uma ausência de associações entre o peso ao nascer e qualquer indicador de risco metabólico (Hulman et al., 1998), enquanto que outro estudo (Skilton et al., 2014) reportou que indivíduos nascidos com peso elevado não apresentaram diferenças nos níveis de PCR aos 32 anos de

idade, bem como no metabolismo da glicose e perfil lipídico, relativamente àqueles que nasceram com peso considerado normal.

O *Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents,* do *National Heart, Lung, and Blood Institute (2011)*, publicou orientações integradas para a redução do risco cardiovascular em crianças e adolescentes, recomendando nesse sentido o rastreio universal para os níveis de colesterol sanguíneo, entre as idades dos 9 e 11 anos e dos 17 aos 21 anos. Alguns estudos com crianças e adolescentes têm vindo a reportar associações entre o excesso de peso ou obesidade e níveis mais elevados de lípidos e lipoproteínas (Daniels & Greer, 2008; Giordano et al., 2011), e, tal como se pode observar em resultados do *Bogalusa Study* (Berenson et al., 1998), elevações das concentrações de colesterol total (CT), lipoproteínas de baixa densidade (LDL), e triglicerídeos, bem como concentrações mais reduzidas de lipoproteínas de alta densidade (HDL) durante a infância, mostraram-se significativamente associadas *a posteriori* a uma maior prevalência (cerca de 70%) de lesões ateroscleróticas em jovens adultos. Também o rácio CT/HDL tem vindo a ser utilizado como um índice aterogénico (Expert Panel on Detection, 2001). No entanto, apesar de alguns autores (Lemieux et al., 2001; Millan et al., 2009) considerarem que a variação no rácio CT/HDL pode estar associada a alterações mais substanciais nos índices metabólicos preditivos de risco de doença cardíaca isquémica e de resistência à insulina do que outros indicadores do perfil lipídico, particularmente as LDL, este indicador parece ainda estar pouco explorado, nomeadamente em estudos com crianças e adolescentes (Agirbasli et al., 2015; Lobelo et al., 2009).

Libby et al. (2008) não observaram associações entre o peso ao nascer e os níveis de CT em jovens adultos, enquanto Skidmore et al. (2004) reportaram apenas um pequeno efeito desse indicador antropométrico precoce nos níveis de CT de homens com uma média de idades de 53 anos, com um impacto na saúde muito limitado; não se verificaram mais associações entre os outros indicadores lipídicos analisados (LDL e HDL) em ambos os sexos. No mesmo sentido, alguns estudos com crianças e adolescentes (Horta et al.,

2009; Kim et al., 2006; Kuhle et al., 2017; Lawlor et al., 2005; Murtaugh et al., 2003) têm vindo a reportar uma ausência de associações significativas entre o peso ao nascer e os valores de CT, LDL, HDL e triglicerídeos. Em jeito de consolidação do exposto anteriormente, uma revisão sistemática (Huxley et al., 2004) concluiu que um eventual subdesenvolvimento fetal não parece exercer efeitos sobre os níveis de CT, de maneira a que tenham um impacto significativo no aumento do risco de doença cardiovascular. Este corpo de conhecimento vai sugerindo que a relação entre o desenvolvimento fetal, reflectido pelo peso ao nascer, e os níveis de CT em adolescentes parece ser fraca e provavelmente de importância limitada para a saúde pública, em comparação com os efeitos que a manutenção da obesidade pode ir exercendo no decorrer da infância (Owen et al., 2003).

Tem vindo a ser descrito que, para além de níveis mais elevados de alguns biomarcadores inflamatórios (DeBoer, 2013) e de um perfil lipídico desfavorável (Daniels & Greer, 2008), indivíduos com excesso de peso ou obesidade usualmente também apresentam um metabolismo da glicose menos eficiente (D'Adamo & Caprio, 2011). Neste sentido, o aumento dos níveis de adiposidade explicou 72% do aumento da prevalência de diabetes nos Estados Unidos entre 1988 e 2014, e os resultados foram consistentes para homens e mulheres (Stokes & Preston, 2017). A concomitante persistência de níveis elevados de alguns biomarcadores inflamatórios em indivíduos com excesso de peso ou obesidade, reflete um estado de inflamação sistémica e crónica de baixo grau, que também parece desempenhar uma função na patogénese da resistência à insulina e na diabetes tipo 2 (Calder et al., 2013; Esser et al., 2014).

O *Homeostatic Model Assessment of Insulin Resistance* (HOMA–IR) (Matthews et al., 1985) é usado como uma medida válida da resistência à insulina em crianças e adolescentes não diabéticos (Gungor et al., 2004), e geralmente apresenta valores mais elevados em crianças com excesso de peso/obesidade (Gonzalez-Jimenez et al., 2016; Lee et al., 2006). Sabendo-se que a resistência à insulina é o melhor preditor da diabetes, e que surge vários anos antes que a doença se inicie (D'Adamo & Caprio, 2011), a identificação

precoce da patologia inicial, no sentido de prevenir e/ou gerir a doença, parece revestir-se de grande importância.

No entanto, os resultados que relacionam a resistência à insulina com indicadores antropométricos tão precoces quanto o peso ao nascer, não surgem todos no mesmo sentido. Alguns estudos demonstraram que o peso ao nascer não se mostrou relacionado com a resistência à insulina (HOMA–IR), quer em crianças com 8 anos de idade (Jeffery et al., 2006), quer em adolescentes com uma média de idades de 15 anos (Murtaugh et al., 2003). Outros estudos com crianças e adolescentes têm reportado associações inversas entre o peso ao nascer e resistência à insulina (Kim et al., 2006; Lawlor et al., 2005), bem como associações em forma de U entre o peso ao nascer e posterior risco de diabetes tipo 2 na faixa etária entre os 6 e os 18 anos (Wei et al., 2003). Uma meta-análise (Harder et al., 2007) concluiu no mesmo sentido que este último estudo.

Em populações adultas, alguns resultados demonstram associações inversas entre o peso ao nascer e os valores de HOMA–IR, como se verifica nos trabalhos de Laaksonen et al. (2003) e de Aoyama et al. (2013), enquanto outros (Johnsson et al., 2015) indicam que o peso elevado ao nascer estava associado a um maior risco de diabetes tipo 2 em jovens adultos do sexo masculino.

Ridgway et al. (2011a) também verificaram que crianças e adolescentes nascidos com baixo peso apresentaram índices de HOMA-IR mais elevados, sendo que, no entanto, esta associação só foi observada após ajuste para o perímetro de cintura ou peso atuais. Suportando-se em Lucas et al. (1999), estes autores apresentam como explicação plausível que, quando uma associação entre o peso ao nascer e um parâmetro metabólico (neste caso a resistência à insulina) só é detectada após o ajuste para uma medida de adiposidade, esse facto pode ser indicativo de uma associação com outras variáveis entre o nascimento e uma medição posterior, como por exemplo o ganho rápido de peso. De facto, as associações entre o peso ao nascer e resistência à insulina em períodos futuros podem estar dependentes do

aumento rápido de peso durante os primeiros anos de vida (Fabricius-Bjerre et al., 2011; Ortega et al., 2008a). Ong et al. (2004) verificaram que uma menor sensibilidade à insulina em crianças com 8 anos de idade estava associada a um menor peso ao nascer, mas somente naquelas que pertenciam ao tertil mais elevado de IMC. Dados provenientes da coorte mais jovem do *Helsinki Birth Cohort Study*, com indivíduos nascidos entre 1934 e 1944, também demonstraram que o aumento rápido do IMC após os 2 anos de idade aumentou o risco de diabetes tipo 2 enquanto adultos (Eriksson et al., 2003). Por outro lado, Larnkjaer et al. (2010) verificaram que os ganhos de peso desde o nascimento até aos 9 meses de idade não se associaram com os valores de HOMA-IR aos 17 anos de idade. Também Jeffery et al. (2006) encontraram resultados no mesmo sentido, verificando que o ganho de peso durante as 6 primeiras semanas de vida não se mostrou relacionado com a resistência à insulina estimada pelo HOMA–IR em crianças com 8 anos de idade.

O exposto anteriormente realça a necessidade de investigação adicional para determinar até que ponto as associações entre o peso ao nascer e alguns parâmetros relacionados com a saúde refletem de facto uma programação *in utero*, ou se serão devidas a características do desenvolvimento durante a infância, ou mesmo a fatores genéticos (Lucas et al., 1999; Sattar et al., 2004). Como tal, parte da investigação também se tem debruçado na análise de outros indicadores antropométricos precoces para além do peso ao nascer. Resultados obtidos em estudos levados a cabo com coortes nascidas em períodos mais antigos (Barker et al., 1992; Eriksson et al., 2001b; Fall et al., 1992; Forsen et al., 2004), sugerem que um baixo peso no primeiro ano de idade foi associado a um maior risco de doença coronária na idade adulta, caracterizado por concentrações elevadas de fibrinogénio plasmático, CT e LDL, independentemente do peso ao nascer.

Kerkhof et al. (2012) verificaram que ganhos de peso em relação ao comprimento nos primeiros três meses de vida, mas não o peso ao nascer, se associaram a uma maior prevalência da síndrome metabólica aos 21 anos de idade. Outros estudos demonstraram que o aumento rápido de peso ao longo

dos 2 primeiros anos de vida estava positivamente relacionado com o aumento das concentrações de leptina aos 10 anos de idade, mas não com as de adiponectina (Flexeder et al., 2014). Uma situação inversa relativamente a estes dois biomarcadores foi observada no estudo de Larnkjaer et al. (2010), tendo os autores verificado que os ganhos de peso desde o nascimento até aos 9 meses de idade não se relacionaram com os valores de leptina aos 17 anos de idade, mas associaram-se negativamente com os níveis de adiponectina. Também aumentos rápidos de peso após o segundo ano de vida de jovens adultos do sexo masculino, e após o quarto ano em mulheres da mesma faixa etária, foram associados a níveis elevados de PCR (> 3 mg/L) aos 23 anos de idade (Nazmi et al., 2009).

No mesmo sentido encontram-se os resultados de Leunissen e colaboradores relativamente ao perfil lipídico. Os resultados de um estudo (Leunissen et al., 2009a) desse grupo de trabalho sugerem que um rápido ganho de peso durante os três primeiros meses de vida se associa positivamente com os níveis de triglicerídeos e com o rácio CT/HDL, bem como inversamente com os de HDL, aos 21 anos. Outro trabalho dos mesmos autores (Leunissen et al., 2008) especificou que a acumulação excessiva de massa gorda durante a infância de um indivíduo influencia significativamente os seus níveis de CT, LDL, HDL e triglicerídeos aos 21 anos de idade, enquanto que o peso ao nascer parece não ter nenhuma contribuição neste sentido. Também no estudo de Bekkers et al. (2011) foi reportado que tanto o baixo como o elevado peso ao nascer não se associaram com os valores de CT, HDL e rácio CT/HDL avaliados aos 8 anos de idade, mas por outro lado verificaram que um padrão de crescimento caracterizado por um rápido ganho de peso durante o primeiro ano de vida se associava positivamente com o rácio CT/HDL aos 8 anos.

Da mesma forma que a adiposidade excessiva é considerada um fator determinante para o desenvolvimento de uma série de doenças cardiometabólicas (Heymsfield & Wadden, 2017), também níveis reduzidos de aptidão física e de atividade física e maior tempo sedentário têm sido associados, de uma forma genérica, a uma série de parâmetros negativos relacionados com a saúde (Artero et al., 2011; Carson et al., 2016; Katzmarzyk, 2010; Ortega et al., 2008b; Poitras et al., 2016). Por exemplo, no estudo de Carnethon et al. (2003), foi reportado que adolescentes com baixa aptidão cardiorrespiratória (abaixo do percentil 20) tinham três a seis vezes mais probabilidades de desenvolver síndrome metabólica, diabetes e hipertensão arterial, do que adolescentes com elevada aptidão cardiorrespiratória (acima do percentil 60).

O conceito de aptidão física pode ser definido como um conjunto de atributos que as pessoas têm, ou que adquirem, relacionados com a capacidade de realizar atividade ou exercício físico (U.S. Department of Health and Human Services, 1996). A aptidão cardiorrespiratória é uma dimensão da aptidão física, e representa uma medida da capacidade aeróbia funcional, refletindo a eficiência dos sistemas respiratórios e circulatórios do corpo humano no fornecimento de oxigénio e energia aos órgãos e estruturas, durante atividades físicas continuadas, e que envolvam grandes grupos musculares (Institute of Medicine, 2012), representada normativamente pelo consumo máximo de oxigênio (VO_2max) em mililitros por Kg de peso corporal por minuto ($ml.Kg^{-1}.min^{-1}$).

O teste de espirometria de circuito aberto em ambiente laboratorial é considerado o método *gold standard* para a medição direta do VO_2max. Em alternativa, a aptidão cardiorrespiratória pode ser estimada no terreno de forma relativamente simples através do denominado *shuttle run test (*ou *teste do vaivém)*, tendo este teste demonstrado ser válido, viável e fiável em populações jovens (Ruiz et al., 2011; Stickland et al., 2003). Neste teste é pedido aos participantes que corram em linha reta entre 2 linhas distanciadas a 20 metros uma da outra, mantendo um ritmo constante, encorajando-os a continuar a corrida durante o maior tempo possível, ou seja, até ao ponto de

exaustão. A velocidade inicial de corrida é de 8,5km/h, com incrementos de nível correspondentes a 0,5km/h a cada minuto, anunciados num aparelho de som, atingindo-se os 18km/h ao minuto 20. O teste termina quando o participante não consegue alcançar uma das linhas antes dos sinais áudio por duas ocasiões, ou quando desiste devido a fadiga.

O número de percursos efectuados por cada participante é posteriormente utilizado como uma variável essencial para estimar o VO_2max, com recurso a uma das várias equações existentes (Barnett et al., 1993; Léger et al., 1988; Mahar et al., 2011; Mahar et al., 2006; Matsuzaka et al., 2004), com alguns autores (Léger et al., 1988; Matsuzaka et al., 2004; McVeigh et al., 1995) a sugerirem que o melhor poder preditivo poderá advir daquelas equações que incluem nas suas fórmulas dados relativos ao IMC ou pregas de adiposidade subcutânea, idade e sexo, como por exemplo as de Mahar et al. (2011), Barnett et al. (1993) ou Matsuzaka et al. (2004), relativamente às que apenas incluem a idade e não consideram outras variáveis, como por exemplo a de Leger et al. (1988), sendo esta uma das equações mais utilizadas em estudos epidemiológicos (Melo et al., 2011).

A aptidão cardiorrespiratória é influenciada em grande medida pela componente genética, estimando-se que esse valor esteja na ordem dos 40–50% (Bouchard et al., 1999; Bouchard et al., 1998; Bouchard et al., 1986). No entanto, os níveis de aptidão cardiorrespiratória são também influenciados por factores comportamentais. Por exemplo o excesso de peso/obesidade e uma maior percentagem de massa gorda em adolescentes estão normalmente associados a níveis mais baixos de aptidão cardiorrespiratória (Coelho-e-Silva et al., 2013). Por outro lado, a atividade física regular pode também ser um determinante importante da aptidão cardiorrespiratória, uma vez que requer um aumento da quantidade de oxigênio inalado para posterior distribuição pelos tecidos corporais, levando à melhoria da sua eficiência (Salonen et al., 2011), devendo ser levado em conta, no entanto, as fortes evidências de uma heterogeneidade considerável nas respostas de diferentes sujeitos aos estímulos de uma mesma atividade física regular (Bouchard & Rankinen, 2001).

A atividade física é definida como qualquer movimento corporal produzido pela contração muscular esquelética, que aumente o dispêndio energético acima do nível basal (Caspersen et al., 1985). A taxa metabólica de repouso representa, como indicado pela sua denominação, o dispêndio energético do organismo em repouso, que em termos de consumo de oxigénio é, por convenção, aproximadamente 3,5 $ml.Kg^{-1}.min^{-1}$, e é habitualmente denominado por *Equivalente Metabólico* [MET (*Metabolic Equivalent Task*)]. A intensidade das atividades físicas é frequentemente classificada recorrendo aos MET como referência, sendo que atividades de intensidade ligeira são definidas como estando no intervalo de 1,1 MET a 2,9 MET; intensidade moderada compreende atividades que se situam entre os 3,0 e os 5,9 MET; atividades de intensidade vigorosa ocorrem acima dos 6,0 MET (Ainsworth et al., 1993).

As recomendações mais recentes da Organização Mundial de Saúde (WHO, 2010) indicam que crianças e adolescentes dos 5 aos 17 anos de idade, devem acumular um mínimo de 60 minutos diários de atividade física que combinem intensidades entre a moderada e a vigorosa, e também que devem ser realizadas atividades de intensidade vigorosa que incorporem exercícios que estimulem o fortalecimento de músculos e ossos, pelo menos 3 vezes por semana; recomendações recentes (Tremblay et al., 2016) incorporam também comportamentos relativos ao tempo sedentário, tais como não ultrapassar as 2 horas por dia de tempo de ecrã, e evitar estar sentado por períodos prolongados, bem como cumprir períodos de sono ininterruptos consoante a faixa etária.

Contrariamente à avaliação da aptidão cardiorrespiratória, tida como mais simples de se realizar (Ekelund, 2008), a atividade física e o tempo sedentário têm na sua medição um desafio acrescido, uma vez que são considerados comportamentos complexos, condicionados por uma grande variedade de factores (Katzmarzyk, 2010; Sallis et al., 2000). No sentido de tentar colmatar as importantes limitações reconhecidas aos questionários de avaliação dos níveis de atividade física auto-reportada, uma vez que se lhes reconhece baixa sensibilidade, elevada variação, menor precisão e,

frequentemente, uma sobrestimação dos níveis de atividade física (Dyrstad et al., 2014), a utilização de acelerómetros tem vindo a ser cada vez mais uma prática corrente na avaliação da atividade física e do tempo sedentário (Trost et al., 2011), uma vez que permite uma medição direta e objetiva das três dimensões da atividade física (intensidade, frequência e duração), apesar de algumas limitações relativamente a certo de tipo de atividades, como por exemplo andar de bicicleta, ou atividades realizadas em meio aquático.

As associações entre adiposidade e a aptidão cardiorrespiratória, atividade física e tempo sedentário têm vindo a ser bem descritas em estudos transversais (Coelho-e-Silva et al., 2013; Ekelund et al., 2012; Hildebrand et al., 2015; Ortega et al., 2013; Ortega et al., 2007). No entanto, não está ainda completamente estabelecido se, e quão precocemente, alguns indicadores antropométricos precoces se associam longitudinalmente com os níveis de aptidão cardiorrespiratória, atividade física e tempo sedentário em períodos posteriores da vida. Grande parte desta pesquisa concentrou o seu foco na programação fetal e mais especificamente no peso ao nascer (Boreham et al., 2001; Lawlor et al., 2008; Ridgway et al., 2011b), e menos atenção tem sido dedicada ao período de crescimento durante os primeiros anos de vida (Oglund et al., 2015), nomeadamente na influência do desenvolvimento do IMC nas variáveis referidas anteriormente, apesar de se encontrarem alguns trabalhos nesse sentido (Hallal et al., 2012; Hildebrand et al., 2016; Salonen et al., 2011).

Andersen et al. (2009) verificaram que indivíduos que nasceram com baixo ou elevado peso, apresentaram uma menor probabilidade de realizar atividade física durante o tempo de lazer na adolescência; já dentro do intervalo de peso ao nascer considerado normal, os mesmos autores reportaram que a associação entre o peso ao nascer e a atividade física em tempo de lazer foi considerada insignificante. Estudos de Campbell et al. (2010), Mattocks et al. (2008) e Kehoe et al. (2012) não encontraram associações entre o peso ao nascer e níveis de atividade física em períodos futuros. Uma recente revisão sistemática e meta-análise (Oglund et al., 2015) concluiu que, de todos os estudos que mediram objetivamente a atividade física, nenhum deles apresentou associações significativas entre esta variável

e o peso ao nascer. Também os trabalhos de Hallal et al. (2006), Ridgway et al. (2011b) e Pearce et al. (2012) apresentaram conclusões no mesmo sentido, sugerindo que o peso ao nascer parece não ter a capacidade de influenciar os níveis de atividade física durante a infância e a adolescência, mas acrescentam que a mesma tendência se verifica também relativamente ao tempo sedentário.

Um estudo de Gopinath et al. (2013) reportou que o peso ao nascer se associou significativamente com a atividade física total na adolescência, mas que não demonstrou ser um determinante do comportamento sedentário (caracterizado pelo tempo de ecrã). No entanto também existem resultados em sentido contrário, sugerindo que o peso ao nascer está positivamente associado ao tempo sedentário durante a adolescência (Hildebrand et al., 2015), com um aumento de 1 Kg no peso ao nascer a representar mais 4 minutos de tempo sedentário por dia; porém, quando o perímetro de cintura atua como mediador desta associação, a sua significância desaparece. Neste sentido, uma recente revisão sistemática (Hildebrand et al., 2016) concluiu que a maioria dos estudos analisados sugere uma ausência de associações entre o peso ao nascer e o comportamento sedentário em crianças e adolescentes.

Para Touwslager et al. (2013), o peso ao nascer parece ter uma associação em forma de U com a aptidão cardiorrespiratória, sendo que as crianças com os pesos ao nascer mais baixos ou mais elevados foram as que apresentaram um menor consumo máximo de oxigénio na adolescência. Tikanmäki et al. (2017) verificaram que um elevado peso ao nascer está associado com baixos níveis de atividade física e aptidão cardiorrespiratória na adolescência, enquanto que os resultados de van Deutekom et al. (2015) sugerem que o baixo peso ao nascer está associado a menores níveis de aptidão cardiorrespiratória na infância.

Em sentido contrário com os trabalhos referidos anteriormente, Lawlor et al. (2008) verificaram que o peso ao nascer está positivamente associado à aptidão cardiorrespiratória, avaliada em crianças com 9 anos de idade. Resultados mistos foram encontrados no estudo de Boreham et al. (2001). Estes autores verificaram que, por cada diminuição de 1Kg no peso ao nascer,

existiu uma diminuição média de 4,84 percursos e 3,21 percursos no teste de *shuttle run*, em rapazes e raparigas de 12 anos, respetivamente; porém, aos 15 anos de idade, as associações entre o peso ao nascer e a aptidão cardiorrespiratória tornaram-se não significativas. Uma ausência de associações entre o peso ao nascer e a aptidão cardiorrespiratória em adolescentes de ambos os sexos com idades a rondar os 15 anos foi também reportada por Ortega et al. (2009). Também em outros estudos (Laaksonen et al., 2003; Salonen et al., 2011) não foram observadas associações significativas entre o peso ao nascer e a aptidão cardiorrespiratória, tendo em conta que nestes últimos a amostra era composta por indivíduos adultos. Já relativamente ao período de crescimento durante a infância, Salonen et al. (2011) reportaram que este está genericamente associado à aptidão cardiorrespiratória na idade adulta, com um maior IMC aos 11 anos a predizer uma pior aptidão cardiorrespiratória na idade adulta, independentemente dos fatores confundidores. Seria interessante a existência de mais estudos que realizassem uma análise mais detalhada destas relações, nomeadamente através de intervalos mais curtos entre as idades onde o IMC era obtido, tendo em vista um estudo mais pormenorizado das associações entre os primeiros anos de vida e os níveis de aptidão cardiorrespiratória em idades mais avançadas.

Estudos utilizando dados provenientes do *Pelotas 1993 Birth Cohort Study* (Victora et al., 2006; Victora et al., 1996) apresentaram resultados interessantes relativamente a uma eventual influência de fatores fisiológicos durante a infância na programação dos níveis de atividade física na adolescência. Hallal et al. (2006) verificaram que o excesso de peso no primeiro e quarto anos de vida não se revelou um preditor significativo dos níveis de atividade física no período de tempo compreendido entre os 10 e os 12 anos. Num outro estudo (Hallal et al., 2012), utilizando a mesma amostra, não foram encontradas diferenças nos padrões de ganho de peso durante a infância entre adolescentes classificados como ativos ou inativos aos 13,3 anos de idade, sugerindo que esses ganhos de peso, pelo menos até aos 4 anos de

idade, não parecem ser determinantes importantes dos níveis de atividade física na adolescência.

Uma recente revisão sistemática e meta-análise (Oglund et al., 2015) apenas considerou três estudos que examinaram as relações entre o crescimento em idades precoces e a atividade física em períodos futuros. Para além dos de Hallal e colaboradores (Hallal et al., 2012; Hallal et al., 2006), referidos anteriormente, um estudo de Eriksson et al. (2012) verificou que uma alteração na percentagem de massa gorda durante o período temporal entre as 12 semanas e os 18 meses de idade, se correlacionou inversamente com os níveis de atividade física e dispêndio energético medidos aos 18 meses. No entanto, estes estudos diferem bastante na sua metodologia, nomeadamente nos indicadores antropométricos precoces, nas idades, e nos intervalos de tempo em que é avaliada a atividade física, bem como na forma em que a atividade física em si mesma foi também medida. Como tal, a literatura existente acerca das relações entre os indicadores antropométricos durante a infância e os níveis futuros de atividade física parece não ser suficiente para que possam ser tiradas conclusões num determinado sentido.

Numa revisão sistemática (Hildebrand et al., 2016) apenas dois estudos (Fuller-Tyszkiewicz et al., 2012; Hands et al., 2011) foram referenciados como tendo examinado a associação entre o IMC em idades bastante jovens (entre os 2 e os 6 anos) e o tempo sedentário alguns anos mais tarde (estimado em ambos os estudos através do tempo de ecrã reportado pelos pais, e não objectivamente medido através de acelerometria), sendo reportadas associações positivas nos dois casos.

Como se depreende pelo exposto anteriormente, os resultados apresentados pelos vários estudos não são de todo unânimes, o que impede conclusões consistentes acerca das relações existentes entre indicadores antropométricos tão precoces como o peso ao nascer e dos padrões de crescimento nos primeiros anos de vida, e a adiposidade, biomarcadores inflamatórios e metabólicos, a aptidão cardiorrespiratória, a atividade física e o tempo sedentário durante a adolescência.

CAPÍTULO II

OBJETIVOS

Objetivos

A presente tese tem quatro objetivos principais interrelacionados e sequenciais:

1 – Determinar se os indicadores antropométricos desde o nascimento até aos 6 anos de idade possuem capacidade discriminatória de previsão de níveis aumentados de adiposidade na adolescência (Artigo I);

2 – Verificar que medidas de adiposidade possuem capacidade discriminatória na previsão de níveis aumentados de biomarcadores inflamatórios e metabólicos, em adolescentes (Artigo II)

3 – Explorar as associações entre indicadores antropométricos desde o nascimento até aos 6 anos de idade e biomarcadores inflamatórios, resistência à insulina e perfil lipídico na adolescência (Artigo III);

4 – Explorar as associações entre indicadores antropométricos desde o nascimento até aos 6 anos de idade e a aptidão cardiorrespiratória, a atividade física e o tempo sedentário na adolescência (Artigo IV).

Na persecução dos objetivos acima mencionados, foram realizados quatro artigos originais, que são de seguida apresentados:

Artigo Original I

Título: Diagnostic Ability of Birth Weight and Early Life Body Mass Index on Adiposity During Adolescence: the LabMed Physical Activity Study.

Autores: José Oliveira-Santos, Rute Santos, Carla Moreira, Sandra Abreu, Luís Lopes, César Agostinis-Sobrinho & Jorge Mota

Objetivos: Avaliar a capacidade do peso ao nascer e do IMC desde o nascimento até aos 6 anos de idade, para discriminar um estado desfavorável de adiposidade durante a adolescência, estimado por várias medidas de adiposidade.

Estado: Submetido.

Artigo Original II

Título: Ability Of Measures of Adiposity in Identifying Adverse Levels of Inflammatory and Metabolic Markers in Adolescents.

Autores: José Oliveira-Santos, Rute Santos, Carla Moreira, Sandra Abreu, Luís Lopes, César Agostinis & Jorge Mota

Objetivos: Examinar e comparar diferentes medidas de adiposidade geral e abdominal, em relação à sua capacidade para discriminar níveis aumentados de biomarcadores inflamatórios e metabólicos numa amostra de adolescentes portugueses.

Estado: Publicado.

Oliveira-Santos, J., Santos, R., Moreira, C., Abreu, S., Lopes, L., Agostinis, C., & Mota, J. (2016). Ability of Measures of Adiposity in Identifying Adverse Levels of Inflammatory and Metabolic Markers in Adolescents. *Childhood Obesity, 12*(2), 135-143.

Artigo Original III

Título: Associations Between Early Life Anthropometric Indicators and Low-Grade Inflammation, Insulin Resistance and Lipid Profile During Adolescence: the LabMed Physical Activity Study.

Autores: José Oliveira-Santos, Rute Santos, Carla Moreira, Sandra Abreu, Luís Lopes, César Agostinis-Sobrinho, Gareth Stratton & Jorge Mota

Objetivos: Avaliar as associações entre os indicadores antropométricos precoces como o peso ao nascer e o IMC em várias idades (6,12 e 18 meses e 2, 3, 4, 5 e 6 anos), com biomarcadores de inflamação de baixo grau, resistência à insulina e perfis lipídicos na adolescência.

Estado: Submetido.

Artigo Original IV

Título: Associations Between Early Life Anthropometric Indicators and Cardiorespiratory Fitness, Physical Activity and Sedentary Time in Adolescence.

Autores: José Oliveira-Santos, Rute Santos, Carla Moreira, Sandra Abreu, Luís Lopes, César Agostinis-Sobrinho & Jorge Mota

Objetivos: Explorar as associações entre os indicadores antropométricos precoces como o peso ao nascer ou o IMC em várias idades (6, 12 e 18 meses e 2, 3, 4, 5 e 6 anos) e posteriores níveis de aptidão cardiorrespiratória, atividade física e tempo sedentário na adolescência.

Estado: Submetido.

CAPÍTULO III

MÉTODOS

Desenho do Estudo e Amostra

Uma descrição completa e detalhada dos métodos, procedimentos, medidas e instrumentos utilizados nos trabalhos incluídos nesta tese pode ser verificada em cada um dos artigos que a compõem, sendo aqui disponibilizada apenas uma visão geral e resumida das variáveis utilizadas nos artigos originais e dos procedimentos na sua recolha.

Os artigos realizados no âmbito desta tese utilizaram dados provenientes da avaliação inicial do *Longitudinal Analysis of Biomarkers and Environmental Determinants of Physical Activity Study (LabMed Physical Activity Study)*. Este trata-se de um estudo longitudinal realizado em cinco escolas do norte e centro de Portugal, que visou principalmente avaliar as associações independentes e combinadas da ingestão alimentar e dos níveis de aptidão física nos valores de pressão arterial de adolescentes, durante 2 anos [avaliação inicial (outono de 2011); *follow-up* (outono de 2012); avaliação final (outono de 2013)]. As escolas que integraram o estudo tinham já acordos de colaboração estabelecidos com o CIAFEL e, portanto, foram selecionadas principalmente por razões de conveniência orçamental e logística.

No sentido de evitar qualquer sentimento discriminatório, todos os alunos matriculados nas turmas dos 7º e 10º anos dessas escolas (n = 1678) foram convidados a integrar o estudo, sendo que 1229 adolescentes aceitaram participar. Porém, apenas foram considerados para as análises desta tese indivíduos aparentemente saudáveis, e não portadores de alguma patologia ou doença, ou condição impeditiva da realização dos testes aquando da avaliação inicial. Após a verificação e cumprimento destes critérios, 1017 adolescentes com idades compreendidas entre os 12 e os 18 anos compuseram a amostra da avaliação inicial, e a todos eles foram aplicadas uma bateria de avaliações visando uma série de variáveis, que pelo seu elevado número não serão exaustivamente listadas aqui, referindo-se as seguintes com relevância para a realização desta tese:

- Antropométricas: peso corporal, estatura (e posterior cálculo do IMC), estatura sentado; percentagem de massa gorda estimada por

bioimpedância; perímetro de cintura (e posterior cálculo do rácio cintura/estatura);

- Aptidão física: realização do *shutlle run test*, para posterior estimação da aptidão cardiorrespiratória;
- Maturação sexual: de acordo com a classificação de Tanner (1962), baseada nos caracteres sexuais externos primários e secundários.
- Estatuto socioeconómico, através da *Family Affluence Scale* (FAS) (Currie et al., 2008).
- Adesão a um padrão de dieta Mediterrânica, através do KIDMED index para crianças e adolescentes (Serra-Majem et al., 2004).

Partindo do número amostral inicial (n=1017) com informação relativa às variáveis referidas anteriormente:

- 539 adolescentes (292 meninas, 247 meninos, idade média 13,9 ± 1,6 anos) conseguiram providenciar os seus *Boletins de Saúde Infantil e Juvenil*, documento oficial do Ministério da Saúde de Portugal, dos quais foram extraídos dados referentes aos períodos da gravidez, pré-natal, perinatal, pós-natal e de crescimento nos primeiros anos de vida, registados pelos médicos durante as consultas regulares;
- 534 adolescentes concordaram em participar nas recolhas sanguíneas; após análise dos resultados, 5 foram excluídos por evidenciarem valores de proteína C-reativa de alta sensibilidade superiores a 10mg/L, o que poderá ser indicativo de um processo inflamatório em curso ou doença (Ridker, 2003). Desta forma, 529 adolescentes (267 raparigas, 262 rapazes) constituíram a amostra final com dados bioquímicos;
- a 587 adolescentes (297 raparigas, 290 rapazes) foram recolhidos dados relativos à atividade física e ao tempo sedentário através de acelerometria.

Análise Estatística

Todas as análises estatísticas foram realizadas através do software *Statistical Package for Social Sciences* (SPSS) versões 22 a 24 (IBM, Armonk,

NY); o software estatístico MedCalc versão 15 (MedCalc, Mariakerke, Bélgica) foi utilizado para as análises das curvas ROC.

O nível de significância para todas a análises foi estabelecido a 0.05.

A tabela 1 indica os procedimentos estatísticos aplicados nos diversos artigos originais desta tese.

Tabela 1. Procedimentos estatísticos aplicados nos artigos originais

	Artigo I	Artigo II	Artigo III	Artigo IV
Teste *t* de Student	x	x	x	x
Teste do Qui-Quadrado			x	x
Curvas ROC	x	x		
Correlações parciais			x	
ANCOVA			x	x
Regressões lineares múltiplas			x	x

Procedimentos Éticos e Legais

Todos os trabalhos realizados no âmbito desta tese foram aprovados pela Comissão de Ética da Faculdade de Desporto da Universidade do Porto através do processo CEFADE 01.2014, e conduzidos de acordo com a *Helsinki Declaration for Human Studies* de 1975, revista em 2013 (World Medical Association, 2013).

O *LabMed Physical Activity Study* foi aprovado pela Autoridade Portuguesa de Proteção de Dados (nº 1112434/2011) e pelo Ministério da Ciência e Educação (0246200001/2011). Todas as avaliações foram efectuadas durante os horários das aulas de Educação Física por pesquisadores treinados que compunham o grupo de trabalho do *LabMed Physical Activity Study*.

Todos os participantes foram previamente informados sobre os objetivos do estudo. Foram obtidos consentimentos informados por escrito junto dos adolescentes e seus pais ou tutores legais.

CAPÍTULO IV

ARTIGOS ORIGINAIS

Artigo Original I

Diagnostic Ability of Birth Weight and Early Life Body Mass Index on Adiposity During Adolescence: the LabMed Physical Activity Study

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Submetido.

ABSTRACT

Introduction: Tracking of excessive adiposity from early childhood into adolescence and adulthood has been studied. However, it remains unclear which is the critical period to start preventing overweight and obesity later in life. We aimed to assess the ability of birth weight, body mass index (BMI) at birth, and BMI from 6 months up to 6 years of age in diagnosing an unfavourable status of several adiposity measures in adolescents.

Methods: A retrospective school-based study with 539 Portuguese adolescents (292 girls, 247 boys) with a mean age of 13.94 ± 1.62 years took.

Anthropometric data on birth and early growth were extracted from individual child health book records. Actual weight, height and waist circumference were measured, and BMI and waist-to-height ratio were calculated. Body fat percentage was estimated by bioelectrical impedance. Adolescents were classified as normal or overweight/obese/overfat for the several adiposity measures according to national and international reference values.

Receiver operating characteristic curves were used to explore the ability of birth weight, BMI at birth, and BMI at 6, 12, 18 months, and at 2, 3, 4, 5 and 6 years of age to diagnose an unfavourable status for each adiposity measure in adolescence.

Results: Birth weight and BMI at birth presented no discriminatory ability for any of the unfavourable categories of adiposity in adolescents of both sexes; from 6 months of age onwards it was possible to verify a growing trend for the explanatory power of early BMI at each time point as children get older. The time points were BMI presented higher discriminatory ability for all the adiposity measures were at 5 years old for girls, and 6 at years old for boys, enhancing the importance that must be given to this growth period for preventing overweight and obesity later in adolescence.

Conclusion: Our results highlight the utility of BMI screening at early ages in correctly classify adolescents in unfavourable categories of several adiposity measures.

KEYWORDS: Adolescents, early life, adiposity, ROC curves.

INTRODUCTION

Tracking adiposity from early childhood into adolescence and adulthood has been carefully studied (Evensen et al., 2016; Freitas et al., 2012), due to its apparent associations with several cardiometabolic abnormalities (Juonala et al., 2011; Twig et al., 2016). However, there is still no consensus on the strength of the associations between early life determinants such as low birth weight (BW), high BW or high body mass index (BMI) during growth in the first years of life, and later overweight and obesity (Evensen et al., 2016; Leunissen et al., 2009). In addition, it also remains unclear how early the ideal period to start preventing overweight and obesity later in life should be determined (Evensen et al., 2016; Ong, 2006).

BW is frequently used as a proxy measure of intrauterine growth and has been associated with body composition throughout an individual's life, although there are inconsistent results and different positions about if, and how, BW influences the risk of childhood obesity and later health related-outcomes. Some authors have proposed a J-shaped (Parsons et al., 2001) or a U-shaped (Qiao et al., 2015) curve association between birth weight and the risk of later obesity.

Low BW has been frequently described as an important contributor for impaired future health (Chen et al., 2012; Vaag, 2009), but its associations regarding future obesity are controversial. Some studies have found that low BW was associated with a reduced risk of obesity (Rooney et al., 2011; Ye et al., 2010); whereas others have showed an increased risk (Dubois & Girard, 2006), or even no associations (Rugholm et al., 2005). On the other hand, high BW has been consistently associated with a higher risk of later overweight/obesity (Johnsson et al., 2015), in studies with both girls and boys at the age of 4–5 years (Oldroyd et al., 2011) and at the age of 9–11-year-old (Qiao et al., 2015).

However, some authors have questioned the importance attributed to BW in relation to future overweight or obesity, arguing that these may be more strongly associated with rapid growth during childhood, than with size at birth

per se (Leunissen et al., 2009; Monteiro et al., 2003). For example, a study of Parsons et al. (2001) have showed that for boys who grew rapidly, the risk of obesity in adulthood was similar for those born either with low or high BW.

Furthermore, most of the research on the early life determinants of later overweight and obesity has been taken considering an unfavourable condition indicated solely by a high BMI. Although BMI is probably the most widely used anthropometric index to define weight status in large samples (Cole et al., 2000; WHO, 2000), additional information on other measures of adiposity such as body fat percentage (BF%), waist circumference (WC) and waist-to-height ratio (WHtR) would provide a more complete and reliable characterization of each adolescent adiposity status, and a more comprehensive view of this phenomenon.

To the best of our knowledge, no similar methodological approach has been taken previously. As such, we aimed to assess and compare the discriminatory ability of BW and BMI at birth and at several time points of age (6, 12 and 18 months, and at 2, 3, 4, 5 and 6 years of age), in classifying correctly individuals in an unfavourable category, assessed by several adiposity measures, such as BMI, BF%, WC and WHtR during adolescence.

SUBJECTS, MATERIALS AND METHODS

Study design and sampling

This study used data from the Longitudinal Analysis of Biomarkers and Environmental Determinants of Physical Activity Study (LabMed Physical Activity Study), a retrospective cohort study carried out in five schools in the north of Portugal, which aimed primarily to evaluate the independent and combined associations of dietary intake and fitness levels on blood pressure levels of adolescents. A detailed description of the study protocol and procedures can be found elsewhere (Oliveira-Santos et al., 2016). Briefly, baseline data was collected in the fall of 2011, from an initial sample of 1229 apparently healthy adolescents (12–18 years old) that agreed to participate in that study. Of these, 539 adolescents (292 girls, 247 boys, mean age 13.9±1.6

years) were able to provide the child health booklets records for early life data extraction, constituting the final sample for the present study. This number fulfils the condition of a Receiver Operating Characteristic (ROC) curves sample size calculation (providing 80% power at 5% significance, for a minimum expected area under the curve (AUC) of 0.6 and null hypothesis value of 0.5), requiring at least 514 subjects for the analyses.

This study was conducted in accordance to the Helsinki Declaration for Human Studies of 1975, as revised in 2013 (World Medical Association, 2013), and approved by the Portuguese Data Protection Authority (#1112434/2011) and the Portuguese Ministry of Science and Education (0246200001/2011). All participants were previously informed of this study aims, and all procedures were carried out with the adequate agreement of the subjects, and written informed consent was obtained from participating adolescents and their parents/tutors.

Early life data

Information on pregnancy, prenatal, birth, postnatal and growth periods was retrospectively collected from individual child health booklets records called *Boletim de Saúde Infantil e Juvenil*, provided by the participants. All weight, length and height measurements from birth up until the age of 6 years were performed and registered on the health booklets by the paediatricians during regular appointments with the participants, and were extracted for the present analysis. BMI from birth until the age of 2 years was calculated as weight divided by length squared (Kg/m^2), and from 2 years onward calculated as usual (weight divided by squared height [Kg/m^2]). All the participants of this study cohort were born between 1993 and 2000.

Anthropometric measurements

Anthropometric measures were collected according standardized procedures (Lohman et al., 1988). BMI was then calculated as previously

described, and the participants were classified in two categories as underweight/normal weight or overweight/obese, using the age and sex-specific BMI-for-age percentiles cut-off values proposed by the World Health Organization (WHO, 2007).

BF% was estimated by bioelectrical impedance (Tanita InnerScan BC532, Tokyo, Japan). After manual introduction of the sex, age and height into the scale system, participants were asked to come up and remain still on the scale until measurement was completed, fulfilling the manufacturer's instructions. This device is suitable for measuring body fat percentage from 7 years onward according to the instruction manual, and has already been used for the same purpose in other studies with adolescents (Abreu et al., 2014; Oliveira-Santos et al., 2016). Given that previous research (Dixon et al., 2013; Goss et al., 2003) has shown inconsistent data on the effects of hydration status and recent exercise on BIA derived body composition measurements, we asked participants to fast overnight, not to drink any fluid four hours prior to their test, urinate within 30 min of test and not to perform any physical exercise in that morning, in order to minimize eventual errors and variations in the BF% assessment. Adolescents were categorized into a normal or overfat/obese category according to McCarthy's body fat reference curves (McCarthy et al., 2006).

Waist circumference was measured with the adolescents in a standing position and at the end of a normal expiration, using a non-elastic tape measure, to the nearest 0.1 cm, midway between the lower rib margin and the anterior superior iliac spine. Waist circumference percentiles for Portuguese adolescents (Sardinha et al., 2012) were used to classify adolescents as normal or obese considering abdominal obesity.

WHtR was calculated as the WC divided by height, both measured in centimetres. The cut-off of 0.5 was used to indicate normal *vs* overfat adolescents, as previously proposed by several authors (Garnett et al., 2008; McCarthy & Ashwell, 2006; Nambiar et al., 2009), where values greater than this cut off point were indicative of increased health risks associated to

abdominal adiposity, in youth as young as five years old and age and sex independent.

Statistical analyses

Descriptive statistics are presented as means and standard deviations (SD). Two-sided Student's t-Test was used to compare groups for continuous variables.

For each adiposity measure, adolescents were categorized as belonging to the normal or overweight/obese/overfat group, according widely used international and national references for BMI (WHO, 2007), BF% (McCarthy et al., 2006), WC (Sardinha et al., 2012) and WHtR (McCarthy & Ashwell, 2006), with overweight/obese/overfat representing the unfavourable category. ROC curves were then used to analyse the discriminatory ability of birth weight, BMI at birth and BMI at 6, 12 and 18 months, and at 2, 3, 4, 5 and 6 years of age, in correctly classifying the adolescents in normal or overweight/obese/overfat categories for each adiposity measure, suggesting the best trade-off between sensitivity and specificity for each early determinant and respective cut-off value. The AUC ranges between 0 and 1 (a worthless and a perfect test, respectively), and represents the ability of the test to correctly classify the participants in a normal or unfavourable category. When the AUC is cumulatively >0.5 and p value <0.05, the ROC curve is considered as having discriminatory ability. The higher the AUC, the better prediction power the model has. The cut-off points were chosen based in the highest Youden index.

Replication of the analysis without twins (n=13, 2.4%) and preterm deliveries (n=39, 7.2%), which could hypothetically represent a foetal sub development, did not presented any different result, as other studies have also (Peneau et al., 2011). Therefore, for the present report we included all the 539 participants.

Data was analysed using the Statistical Package for Social Sciences version 24.0 (SPSS, IBM Corp., NY, USA), and MedCalc statistical software version 15 (MedCalc software, Mariakerke, Belgium) was used for all the ROC

curves analyses, as well as for the sample size calculation. A *p*-value <0.05 was considered to denote statistical significance.

RESULTS

Participants' characteristics are shown in Table 1. Boys were taller, heavier, and had higher WC than girls, while girls presented higher values of BF% ($p<0.05$ for all). In relation to early life data, boys presented significantly higher values on BW, birth length, BMI at birth and BMI at 6, 12 and 18 months of age ($p<0.05$ for all).

Table 1. Characteristics of the Participants at Early Life and Adolescence Periods

	All (*n* = 539)	**Girls (*n* = 292)**	**Boys (*n* = 247)**
Variables	Mean (SD)	Mean (SD)	Mean (SD)
Age (years)	13.94 (1.62)	13.98 (1.63)	13.89 (1.61)
Height (cm)	158.7 (9.00)	156.8 (6.7)	160.9 (10.8) *
Weight (Kg)	53.56 (12.28)	52.16 (10.53)	55.22 (13.92) *
BMI (Kg/m^2)	21.11 (3.73)	21.14 (3.74)	21.09 (3.72)
UW+NW (n; %)	361; 67%	208; 71.2%	153; 61.9%
OW+OB (n; %)	178; 33%	84; 28.8%	94; 38.1%
BF%	21.04 (8.0)	25.06 (6.86)	16.29 (6.52) *
< P85 (n; %)	413; 76.6%	217; 74.3%	196; 79.4%
> P85 (n; %)	126; 23.4%	75; 25.7%	51; 20.6%
WC (cm)	72.5 (9.9)	71.5 (9.6)	73.7 (10.2) *
< P90 (n; %)	449; 83.3%	247; 84.6%	202; 81.8%
> P90 (n; %)	90; 16.7%	45; 15.4%	45; 18.2%
WHtR	0.46 (0.05)	0.46 (0.06)	0.46 (0.06)
< 0.5 (n; %)	422; 78.3%	228; 78.1%	194; 78.5%
> 0.5 (n; %)	117; 21.7%	64; 21.9%	53; 21.5%
Birth Weight (g)	3 772 (482)	3 177 (477)	3 386 (465) *
Birth Length (cm)	49.1 (2.2)	48.6 (2.2)	49.7 (2.0) *
BMI at birth (Kg/m^2)	13.52 (1.39)	13.41 (1.39)	13.66 (1.38) *
BMI at 6 months (Kg/m^2)	17.40 (1.57)	17.09 (1.42)	17.78 (1.65) *
BMI at 12 months (Kg/m^2)	17.72 (1.57)	17.34 (1.41)	18.17 (1.64) *
BMI at 18 months (Kg/m^2)	17.15 (1.43)	16.89 (1.35)	17.45 (1.48) *
BMI at 2 years (Kg/m^2)	16.81 (1.48)	16.70 (1.41)	16.94 (1.55)
BMI at 3 years (Kg/m^2)	16.52 (1.64)	16.39 (1.64)	16.66 (1.63)
BMI at 4 years (Kg/m^2)	16.55 (1.85)	16.45 (1.85)	16.66 (1.86)
BMI at 5 years (Kg/m^2)	16.74 (2.13)	16.67 (2.12)	16.82 (2.15)
BMI at 6 years (Kg/m^2)	17.08 (2.45)	16.89 (2.35)	17.32 (2.56)

*$p < 0.05$ for sex comparisons (two-tailed *t*-test).
Abbreviations: BF%, body fat percentage (McCarthy et al., 2006); BMI, body mass index (WHO, 2007); NW, normal weight; OB, obese; OW, overweight; SD, standard deviation; UW, underweight; WC, waist circumference (Sardinha et al., 2012); WHtR, waist-to-height ratio (McCarthy & Ashwell, 2006).

Figures 1 and 2 represent the ability of BW and BMI at birth and at several time points of age (months 6,12 and 18, and at 2,3, 4, 5 and 6 years) to correctly classify the adolescents into a normal or unfavourable category for BMI, BF%, WC and WHtR, through the AUC values provided by the ROC analysis.

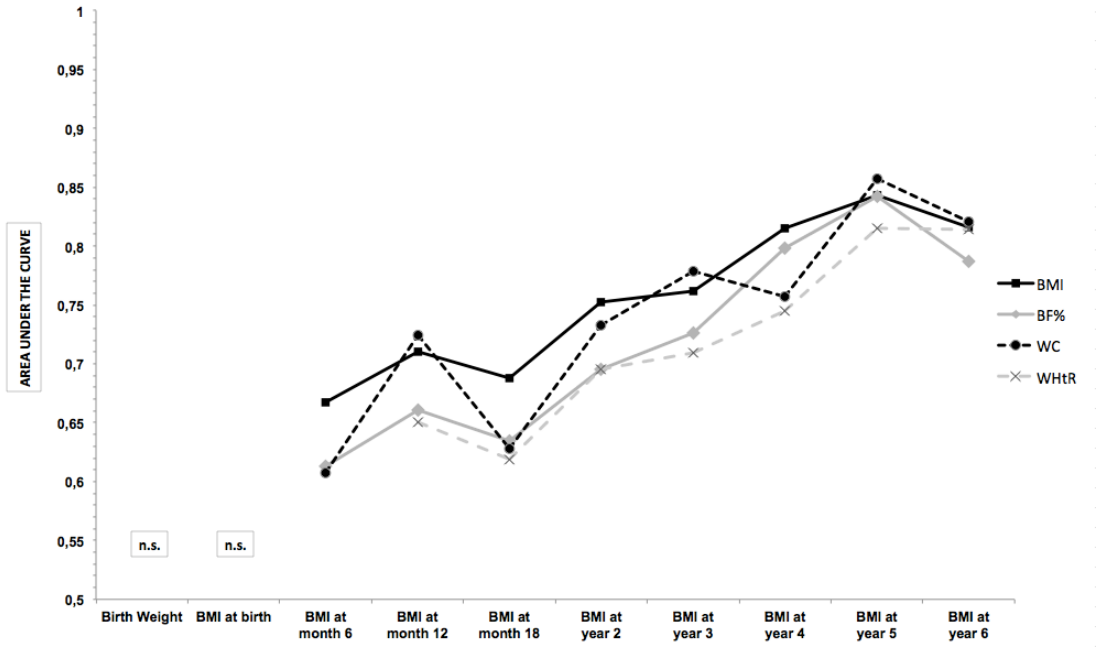

Figure 1. Discriminatory Ability of Birth Weight and Body Mass Index at Several Time Points of Age in Correctly Classifying Adolescent Girls Into a Normal or Unfavourable Category for Each Adiposity Measure

Abbreviations: BMI, body mass index; BF%, body fat percentage; WC, waist circumference; WHtR, waist-to-height ratio; n.s., non-significant area under the curve.

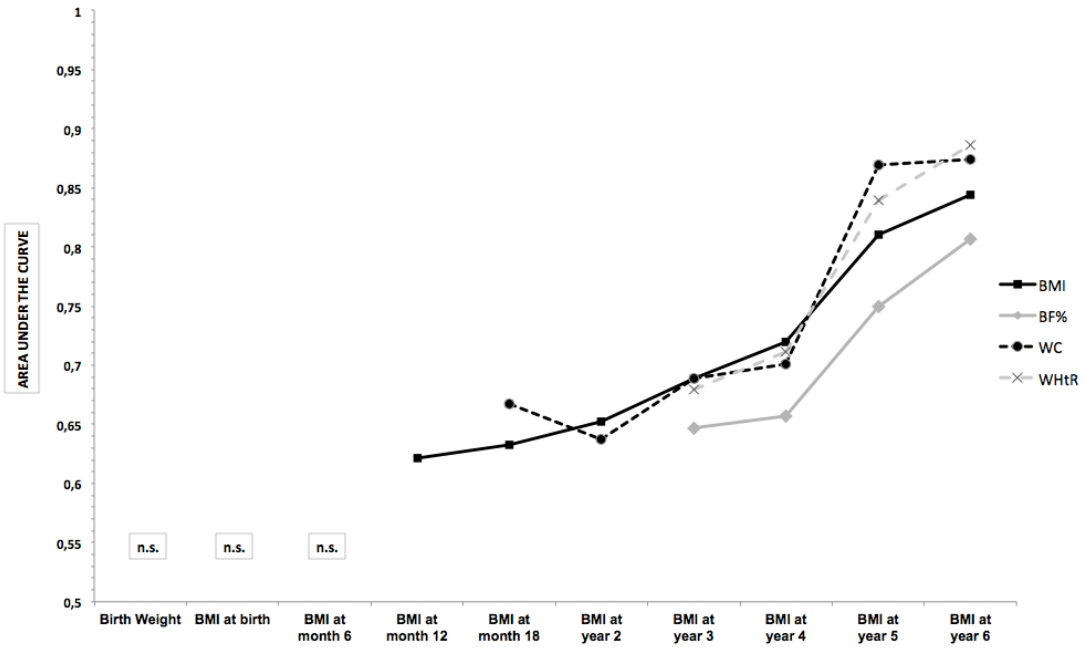

Figure 2. Discriminatory Ability of Birth Weight and Body Mass Index at Several Time Points of Age in Correctly Classifying Adolescent Boys Into a Normal or Unfavourable Category for Each Adiposity Measure
Abbreviations: BMI, body mass index; BF%, body fat percentage; WC, waist circumference; WHtR, waist-to-height ratio; n.s., non-significant area under the curve.

BW and BMI at birth presented no discriminatory ability for any of the unfavourable categories of adiposity in adolescents of both sexes. It was possible to verify a growing trend for the explanatory power of early BMI at each time point as children get older.

In girls, from 6 months to 6 years of age, BMI presented an increasing discriminatory ability for all the adiposity measures in adolescence (except for WHtR at the age of 6 months). 5 years of age was the set point where BMI presented the best discriminatory power for all of the adiposity measures for adolescent's girls.

In boys, BMI at 6 months presented no discriminatory ability for any measure of adiposity; from 12 months of age onwards, BMI presented discriminatory ability for unfavourable BMI at adolescence; from 18 months ahead for WC, and from 3 years onwards for BF% and WHtR.

Table 2. Area Under the Curve and Cut-Off Values of BMI at Each Time Point Presenting Discriminatory Ability for Each Adiposity Measure in Adolescence for Girls

		BMI	BF%	WC	WHtR
Birth weight	AUC	n.s.	n.s.	n.s.	n.s.
	Cut-off (Kg)	–	–	–	–
BMI at birth	AUC	n.s.	n.s.	n.s.	n.s.
	Cut-off (Kg/m2)	–	–	–	–
BMI 6 months	AUC	0.667	0.613	0.607	n.s.
	Cut-off (Kg/m2)	≥16.38	≥16.38	≥16.38	–
BMI 12 months	AUC	0.710	0.661	0.724	0.650
	Cut-off (Kg/m2)	≥16.57	≥17.30	≥17.21	≥17.16
BMI 18 months	AUC	0.688	0.635	0.628	0.619
	Cut-off (Kg/m2)	≥16.53	≥16.40	≥16.10	≥16.53
BMI 2 years	AUC	0.752	0.695	0.733	0.695
	Cut-off (Kg/m2)	≥16.87	≥16.87	≥16.87	≥16.87
BMI 3 years	AUC	0.762	0.726	0.779	0.709
	Cut-off (Kg/m2)	≥17.49	≥17.49	≥16.87	≥17.49
BMI 4 years	AUC	0.815	0.798	0.757	0.745
	Cut-off (Kg/m2)	≥16.64	≥16.40	≥15.91	≥16.98
BMI 5 years	AUC	0.843	0.842	0.857	0.815
	Cut-off (Kg/m2)	≥17.15	≥17.09	≥17.19	≥17.15
BMI 6 years	AUC	0.816	0.787	0.821	0.814
	Cut-off (Kg/m2)	≥17.09	≥17.09	≥17.68	≥17.65

Abbreviations: AUC, Area under the curve; BF%, body fat percentage; BMI, body mass index; WC, waist circumference; WHtR, waist-to-height ratio; n.s., non-significant area under the curve.

Table 3. Area Under the Curve and Cut-Off Values of BMI at Each Time Point Presenting Discriminatory Ability for Each Adiposity Measure in Adolescence for Boys

		BMI	BF%	WC	WHtR
Birth weight	AUC	n.s.	n.s.	n.s.	n.s.
	Cut-off (Kg)	–	–	–	–
BMI at birth	AUC	n.s.	n.s.	n.s.	n.s.
	Cut-off (Kg/m2)	–	–	–	–
BMI 6 months	AUC	n.s.	n.s.	n.s.	n.s.
	Cut-off (Kg/m2)	–	–	–	–
BMI 12 months	AUC	0.621	n.s.	n.s.	n.s.
	Cut-off (Kg/m2)	≥19.07	–	–	–
BMI 18 months	AUC	0.633	n.s.	0.667	n.s.
	Cut-off (Kg/m2)	≥18.07	–	≥18.06	–
BMI 2 years	AUC	0.652	n.s.	0.637	n.s.
	Cut-off (Kg/m2)	≥17.01	–	≥17.64	–
BMI 3 years	AUC	0.689	0.647	0.689	0.679
	Cut-off (Kg/m2)	≥16.83	≥16.83	≥16.79	≥17.39
BMI 4 years	AUC	0.720	0.657	0.701	0.711
	Cut-off (Kg/m2)	≥16.91	≥17.49	≥17.49	≥17.49
BMI 5 years	AUC	0.810	0.750	0.869	0.839
	Cut-off (Kg/m2)	≥16.83	≥18.80	≥16.69	≥16.69
BMI 6 years	AUC	0.844	0.807	0.874	0.886
	Cut-off (Kg/m2)	≥17.42	≥17.60	≥17.60	≥17.60

Abbreviations: AUC, Area under the curve; BF%, body fat percentage; BMI, body mass index; WC, waist circumference; WHtR, waist-to-height ratio; n.s., non-significant area under the curve.

In Table 2 and 3 are presented the valid AUC and correspondent cut-off points suggested by the ROC curves for BMI at each time point, with ability to correctly predict a normal or overweight/obese/overfat category later in adolescence for each adiposity measure and for each sex.

DISCUSSION

The main findings of this study suggest that in relation to the discriminatory ability of early BMI to classify subjects in an unfavourable category of various measures of adiposity later in adolescence, the growth period from 6 months to 6 years of age may be more valuable than the period relative to birth.

Our data shows that the best discriminatory ability time point of early BMI

for all adiposity measures in adolescence was observed at 5 years of age for girls, and at 6 years for boys, with AUC always above 0.8. Regardless of sex, our results also indicate that, as children grew-up, the discriminatory ability for each time point to correctly classify adolescents as normal or overweight/overfat also increases, being tendentiously higher in girls than in boys until the age of 5 years old, and the opposite at the time point of 6 years.

Our results are of importance given that overweight and obesity seem to track throughout life. In a study (Harrington et al., 2010) with overweight patients at age 20, it was found that more than 50% of the participants were overweight at 2 years of age, and all of them were already overweight at age 10. A similar consistent pattern was described by Pietilainen et al. (Pietilainen et al., 2001), who found that subjects who were short and light at birth were still short and light at age 16 years, and conversely those who were long and heavy at birth were tall and heavy at age 16 years.

However, it is not clearly understood how early an unfavourable status relative to a condition of overweight/obesity can predict that same condition years later. Our results have showed that BW and BMI at birth presented no discriminatory ability when trying to predict later overweight/obesity, for any of the adiposity measures studied, in both sexes. Likewise our study, several others have failed to found associations between BW and BMI and other adiposity measures later in adolescence, or have found mixed results (Botton et al., 2008; Dubois & Girard, 2006; Rooney et al., 2011; Rugholm et al., 2005; Ye et al., 2010).

Increased and rapid weight gain during the first years of life have been positively associated with adolescent overweight (Monteiro et al., 2003) and abdominal adiposity (Araújo de França et al., 2014, 2016), and was also associated with a larger impact on measures of body composition (Eriksson et al., 2008) later in life, than the effect of prenatal growth and birth weight and size *per se*, suggesting that infancy could be a more critical period. Studies performed with young adults (Leunissen et al., 2009) and midlife adults (Rolfe et al., 2010) also suggest that rapid postnatal weight gain, rather than birth

weight alone, leads specifically to increased visceral fat in adulthood.

This rapid weight gain in infancy, or “catch-up” growth, is suggested to be a compensatory mechanism following intrauterine growth restraint (Ong et al., 2000; Ounsted & Sleigh, 1975) reflected by a low BW, but has also been associated with larger fat mass, WC and BMI at later ages (Ekelund et al., 2006). However, contradictory data can be found again. Kramer et al. (Kramer, 2014) described that small for gestational age new-borns did not presented higher overall or central adiposity at the age of 11.5 years, regardless of their weight gain trajectories, but rather, it was the larger infants who were predisposed for greater adiposity. At least theoretically, if careful attention is paid on maintaining a balanced pregnancy, with the goal for the baby to be born within the normal weight range (Araújo de França et al., 2016) (i.e., between 2500–4000 grams), this point could be minimized (Schellong et al., 2012). The relatively small percentage of babies born with low weight in developed countries (Ananth & Wen, 2002; Odlind et al., 2003) seems to relativize the importance given to the birth period, in the way that a negative event is not inevitable, and on the other hand, increases the importance of the growth period during early childhood (Rugholm et al., 2005). In our sample, 5.9% of the subjects were born small (<2500g) and 5.2% were born large (>4000g), with 88.9% born within the appropriate BW range, according World Health Oorganization recommendations (WHO & UNICEF, 2004). In addition, many children born within the normal weight range (the vast majority of them) also developed later overweight or obesity, and some of those who were large at birth become normal-weight adolescents (data not shown). Besides, as appointed by Baker et al. (2007), from a public health perspective, focusing on the effect of BMI trajectory is of greater importance because it is modifiable, whereas birth weight is not.

In girls of the present study, BMI started to present discriminatory ability at 6 months of age for all measures of adiposity, except for WHtR, although with AUC’s just slightly higher than 0.6. We also observed a growing trend for the discriminatory ability as years passed by, with a curious slight decrease of the AUC observed at the time point of 18 months of age in comparison to the 12

months, and at 6 years old when comparing with the 5 years old time point.

De Kroon et al. (2011) found that BMI development between 2 and 6 years explained more than 40% of the variance of adult BMI, which is a very considerable value. In addition, Evensen et al. (2016) suggested that high BMI alone, especially at 2–4 years of age, has only a moderate predictive value for overweight and obesity in adolescence; and it was BMI at 6-years of age, corresponding to adult BMI of 27 Kg/m^2 or higher, that predicted overweight/obesity at adolescence with probabilities higher than 50 %. These data is in line with our findings, as in boys from our sample, 6 years of age was the time point where BMI presented its best discriminatory ability, and curiously, with higher AUC for measures of abdominal adiposity [WC (AUC=0.874); WHtR (AUC=0.886)] than for BMI itself (AUC=0.844) and BF% (AUC=0.807).

BMI has been the most widely used index to assess weight status and its health-related risks (Cole et al., 2000; WHO, 2000). The American Academy of Paediatrics (2017) recommends an annual BMI screening as part of preventive primary care for children and adolescents, once there may be children who have not been early recognized as overweight or obese due to the lack of universal screening. Our study reinforces this recommendation, and enhances the potential value of an early BMI screening for a timely identification of later overweight and obesity, once our results were able not only to suggest a strong discriminatory power for an unfavourable BMI in adolescence, but also for other measures of adiposity in either girls and boys, reflected by AUC higher than 0.8 at the ages of 5/6 years.

The strengths of this study include the direct extraction of early life data relative to birth and growth until the age of 6 years old, providing rigorous information for a considerable sample size (n=539). Another strength is that the analysis took into account several measures of adiposity in adolescence, and not only BMI, as usual in most of the studies, which provided us with a more comprehensive assessment of the adiposity status of the adolescents.

However, this study has also some limitations that need to be acknowledged. First, analyses after 6 years of age were not performed due to

the large loss of data related to growth, since routine appointments to the paediatrician are normally not as regular as in the first six years of life, and anthropometric records became sparse; the absence of other measures of adiposity besides weight, length and height collected during early life, did not allowed for WC, WHtR and BF% similar analyses to those performed to evaluate the discriminatory ability of early BMI, which would also provide an interesting analysis, and a more comprehensive view of this phenomenon.

In conclusion, our results highlight the utility of BMI screening at early ages in correctly classify adolescents in unfavourable categories of several adiposity measures. BW and BMI at birth presented no discriminatory ability for any of the unfavourable categories of adiposity in adolescents of both sexes, and in the other hand it was possible to verify a growing trend for the explanatory power of early BMI at each time point, as children get older. The time points of age where BMI presented higher discriminatory ability for all the adiposity measures were at 5 years old for girls, and at 6 years old for boys, enhancing the importance that must be given to this growth period for preventing overweight and obesity later in adolescence.

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Artigo Original II

Ability of Measures of Adiposity in Identifying Adverse Levels of Inflammatory and Metabolic Markers in Adolescents

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Ability of Measures of Adiposity in Identifying Adverse Levels of Inflammatory and Metabolic Markers in Adolescents

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Abstract

Background: Overweight and obesity have been associated with a pro-inflammatory state. We aimed to assess the ability of different measures of overall and abdominal adiposity for identifying adverse levels of inflammatory and metabolic markers in adolescents.

Methods: This is a cross-sectional analysis with 529 Portuguese adolescents (267 girls), mean age 14.3 ± 1.7 years. Weight, height, sitting height, waist circumference (WC), and body fat percentage (BF%) were measured; and BMI, waist-to-height ratio (WHtR), and waist-to-sitting-height ratio (WsHtR) were calculated. We measured C-reactive protein (CRP), fibrinogen, erythrocyte sedimentation rate (ESR), complements C3 and C4, leptin, and adiponectin levels. Receiver operating characteristic (ROC) curves were used to estimate the ability of the adiposity measures to discriminate between low/high values of biomarkers.

Results: The highest areas under the ROC curves were presented by BF% for fibrinogen and complement C3 in both sexes and for ESR, complement C4, and adiponectin only in girls; by BMI for CRP in girls and for leptin in both sexes; by WHtR for leptin in both sexes and for CRP, fibrinogen, and adiponectin only in girls; by waist circumference for CRP, fibrinogen, and complement C3 only in boys and for complement C4 in girls; and by WsHtR for complement C3 in girls; $p < 0.05$ for all.

Conclusions: The measures that more often presented discriminatory power were, for overall adiposity, BF% in both sexes, and for abdominal adiposity, WHtR in girls and WC in boys. However, small differences in discriminatory capabilities don't allow us to clearly defend the adoption of a single measure above all others.

Introduction

Overweight and obesity have been associated with a condition of chronic low-grade systemic inflammation even in children[1,2] and adolescents,[3,4] with evidence of tracking into adulthood,[5,6] contributing to an increased risk of cardiovascular disorders and diabetes[7] over time.

Several anthropometrical measures, indices, and techniques have been used in epidemiological studies to assess obesity in youngsters, as alternatives to more accurate but hardly feasible laboratory assessment, because of the constraints in time, sample mobilization, and high costs.[8] Although BMI is probably the most widely used index to define weight status across populations,[9,10] other techniques also provide information on overall adiposity, such as bioelectric impedance and skinfold measurements, with estimates of body fat percentage (BF%).

In addition, other anthropometric measures have focused on abdominal obesity, a known independent risk factor for insulin resistance and cardiovascular diseases in children and adolescents.[11,12] Low-grade systemic inflammation in youth has been shown to be associated with high waist circumference (WC),[13] waist-to-hip ratio (WHR),[14] and waist-to-height ratio (WHtR).[15] Moreover, individuals with a greater percentage of visceral fat appear to have higher levels of some circulating cytokines and acute-phase reactants than individuals with a higher percentage of subcutaneous fat,[16] suggesting that visceral fat could play a more active role in the development of systemic inflammation. Therefore, the search for one anthropometric measure (or more) that may adequately provide sensitivity and specificity to reflect not only adiposity, but also an adverse inflammatory condition, seems pertinent.

In light of the heterogeneity and lack of previous studies, we aimed to examine and compare different measures of

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overall obesity such as BMI and BF%, and central obesity like WC, WHtR, and waist-to-sitting-height ratio (WsHtR), with respect to their ability to detect increased levels of inflammatory and metabolic markers in a sample of Portuguese adolescents, trying to verify which measure presents the greatest predictive power for each biomarker.

Methods

Study Design and Sampling

We used baseline data from the Longitudinal Analysis of Biomarkers and Environmental Determinants of Physical Activity Study (LabMed Physical Activity Study), a school-based prospective cohort study carried out in five schools from the north of Portugal, which aimed to evaluate the independent and combined associations of dietary intake and fitness levels on blood pressure levels of adolescents. The power calculation for that study was based on the exposure of combined healthy diet/physical activity pattern with a prevalence of 14%.[17] A sample of 754 participants would provide 80% power to detect 15% difference between exposed and unexposed at 5% significance; but taking into account an expected dropout rate of about 20% at each time-point, the minimum sample size was increased to 1086. Baseline data was collected in the fall of 2011, for all pupils that agreed to participate in the study ($n = 1229$). From this initial total sample of apparently healthy adolescents (12–18 years old), 534 agreed to undergo blood collection. Five of them were later excluded from the analysis due to high sensitivity C-reactive protein (CRP) values >10 mg/L, which may be indicative of acute inflammation or illness,[18] leaving 529 adolescents (267 girls, 262 boys, mean age 14.3 ± 1.7 years) as the final sample for the present study. This number fulfills the condition of an ROC sample size calculation (providing 80% power at 5% significance, for a minimum expected AUC of 0.6 and null hypothesis value of 0.5) requiring at least 514 subjects for the present study.

This study was conducted in accordance with the Helsinki Declaration for Human Studies of 1975, as revised in 2008, and approved by the Portuguese Data Protection Authority (#1112434/2011) and the Portuguese Ministry of Science and Education (0246200001/2011). All participants were informed of the study's goals, all procedures were carried out with the adequate understanding of the subjects, and written informed consent was obtained from participating adolescents and their parents/tutors.

Anthropometric Measurements

Anthropometric measurements were performed according to standardized procedures,[19] with all participants lightly dressed in t-shirt, shorts, and barefoot. Body weight was measured to the nearest 0.1 kg, using a portable electronic weight scale (Tanita InnerScan BC532, Tokyo, Japan). Body height was measured to the nearest 0.1 cm, with the adolescent standing upright against a portable stadiometer (Seca213, Hamburg, Germany). BMI was calculated as weight divided to height squared (kg/m^2), and the participants were classified as underweight, normal weight, overweight, or obese using the age- and sex-specific cut-off values proposed by the International Obesity Task Force.[9,20]

Waist circumference was taken in a standing position, midway between the lower rib margin and the anterior superior iliac spine, at the end of a normal expiration, to the nearest 0.1 cm with a nonelastic tape measure. WHtR was calculated as the WC divided by height, both measured in centimeters.

Sitting height was measured with the participant seated on a table, with back and buttocks positioned against a stadiometer and with the head positioned in a Frankfort horizontal plane. The participant's knees were directed straight ahead, with the arms and hands resting at the sides. Sitting height was measured from the tabletop to the vertex and recorded to the nearest 0.1 cm. WsHtR was also calculated as the WC divided by sitting height.

BF% was measured by bioelectrical impedance[21] (Tanita InnerScan BC532) according to manufacturer's instructions, in the morning after an overnight fast for at least 10 hours, and 2 hours after last water intake and urination. Participants were asked not to perform any physical exercise before the measurements that morning. The device used is suitable for measuring BF% in an age range from 7 to 99 years old according the instruction manual, and has been used for the same purpose in other studies with adolescents.[22]

Pubertal Stage Assessment

Pubertal stage (breast and pubic hair development in girls and genital and pubic hair development in boys, with stage 1 being prepubertal and 5 being adult) was self-assessed by the participants according to the classification by Tanner,[23] in a private place, and then communicated to a researcher of the same sex in a closed envelope.

Biochemical Assessment

After an overnight fast (>10 hours), blood samples were collected between 8:00 a.m. and 10:00 a.m. by venipuncture from the antecubital vein. The samples were stored in sterile blood collection tubes in refrigerated conditions (4°C to 8°C) for no longer than four hours during the morning of collection, and then delivered to an analytical laboratory for testing according to standardized procedures, as follows: (1) high sensitivity CRP, latex enhanced immunoturbidimetric assay (Siemens ADVIA 1800, Erlangen, Germany); (2) fibrinogen, Clauss assay (Siemens BCS XP System, Erlangen, Germany); (3) adiponectin and leptin, ELISA (Plate Reader); (4) complement factor C3 (C3) and complement factor C4 (C4), PEG enhanced immunoturbidimetric assay (Siemens ADVIA 1800, Erlangen, Germany); (5) erythrocyte sedimentation rate (ESR), Westergren method (Starrsed, RR Mechanotronics, Netherlands). CRP, C3, C4, adiponectin, and leptin were determined in serum; fibrinogen was determined in plasma;

and ESR was determined in whole blood. The existing literature shows that all the biomarkers analyzed in this study have been increasingly explored in studies involving children or adolescents,[24–27] suggesting that they are a valid choice for this age group.

Statistical Analyses

Two-sided Student's *t*-test was used for comparisons between groups. For each biomarker a z-score was computed by age and sex; and increased levels were considered when the individual had ≥1 SD of the z-score, except for adiponectin, where decreased levels were considered when the individual had ≤−1 SD of the z-score. The setting of ≥1 SD (and ≤−1 SD in the case of adiponectin) allowed us to identify the adolescents of our sample with the highest values for each biomarker (or lowest, in the case of adiponectin), showing two statistically different groups in relation to the biomarkers' mean values (data not shown). Consequently we created two categories for the Receiver Operating Characteristic (ROC) curves analysis.

ROC curves analyzed the ability of different measures of adiposity to discriminate between low/high values of inflammatory and metabolic markers, providing the best trade-off between sensitivity and specificity of each adiposity measure and respective cut-off value. The area under the curve (AUC), ranging between 0 and 1 (a worthless and a perfect test, respectively), represents the ability of the test to correctly classify the participants with high or low inflammatory markers. ROC curves analysis showed which measures of adiposity performed well in identifying increased levels of inflammatory and metabolic markers; AUC >0.5 and $p < 0.05$ indicated that the ROC performed well. Cut-off points were chosen based on the highest Youden index.

Data were analyzed using SPSS 22.0 (IBM, Armonk, NY); MedCalc statistical software version 15 (MedCalc, Mariakerke, Belgium) was used for the ROC curves analyses, including the sample size calculation for this study. A *p*-value <0.05 denoted statistical significance.

Results

Participants' characteristics are shown in Table 1. Boys were heavier, taller, and had higher WC than girls; while girls presented higher values of BF% than boys ($p < 0.05$ for all). In relation to the biomarkers, only CRP values were higher in boys, whereas fibrinogen, adiponectin, erythrocyte sedimentation rate, and leptin were higher in girls ($p < 0.05$ for all).

Tables 2 and 3 present ROC analysis for the associations of measures of overall (BMI and BF%) and abdominal obesity (WC, WHtR, and WsHtR) with biomarkers for girls and boys, respectively. Values in bold represent the ROC curves, indicating the adiposity measures that presented the highest AUC for each biomarker.

BF% was the measure of overall adiposity that more often presented the best discriminatory power for both sexes. Higher levels of fibrinogen were suggested by BF% cut-off values >27.3% for girls and >18.3% for boys, and of C3 by BF% cut-off values >30.7% in girls and >18.2% in boys. BF% also showed discriminatory power for high levels of ESR and C4 and lower levels of adiponectin, but only for girls. BMI presented the best trade-off between sensitivity and specificity for leptin in girls and boys, and for CRP in girls.

Regarding abdominal adiposity, WC presented the best discriminatory power for higher levels of CRP, fibrinogen, and C3 in boys, and for C4 in girls. WHtR showed the best trade-off between sensitivity and specificity for detecting in girls increased levels of CRP, fibrinogen, and adiponectin, and higher levels of leptin in both girls and boys. WsHtR only demonstrated the best discriminatory power for C3 in girls.

Discussion

The main findings of this study showed that for measures of overall adiposity, the highest AUC values were presented by BF% for fibrinogen and complement C3 in both sexes, and for ESR, complement C4, and adiponectin only in girls; and by BMI for CRP in girls and for leptin in both sexes. Regarding measures of abdominal adiposity, the highest AUC values were presented by WHtR for leptin in both sexes and for CRP, fibrinogen, and adiponectin only in girls. The highest AUC values were presented by WC for CRP, fibrinogen, and complement C3 for boys, and for complement C4 in girls; and by WsHtR for complement C3 in girls.

Some studies suggested associations between measures of overall[2,3] and abdominal[28,29] obesity and a series of inflammatory and metabolic markers. However, to the best of our knowledge, there is currently no agreement about which anthropometric measures predict best adverse levels of inflammatory markers, and how they differ by sex. Our results suggest that measures of overall adiposity tended to more often present higher AUC in girls; whereas in boys, higher AUC values were more frequent in measures of abdominal obesity.

Regardless of sex, BF% showed marginally higher differences in the AUC for most of the inflammatory markers compared with BMI. BF% coincided for boys and girls as the measure of overall adiposity that best predicts increased levels of fibrinogen and C3, with slightly higher pooled AUC observed in girls compared to boys, suggesting that discrimination is more precise, on average, in girls. For CRP, ESR, C4, and adiponectin, BF% only showed discriminatory power for girls.

BMI was the best measure of overall adiposity for both sexes, predicting higher levels of leptin, but showing this time an inverse trend, with a higher AUC for boys. In agreement with other studies,[30,31] we found that leptin and adiponectin levels were significantly lower in boys than in girls. It is hypothesized that the increase in testosterone level during male puberty could play an important role in

Table 1. Anthropometric, Biochemical, and Maturational Characteristics of the Participants

	All ($n = 529$)	Girls ($n = 267$)	Boys ($n = 262$)
Variables	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**
Age (years)	14.3 ± 1.7	14.3 ± 1.7	14.4 ± 1.7
Height (cm)	160.3 ± 9.6	157.7 ± 6.7	162.9 ± 11.3*
Weight (kg)	55.2 ± 12.8	53.4 ± 11.2	56.9 ± 14.1*
BMI (kg/m^2) IOTF	21.31 ± 3.84	21.41 ± 3.96	21.20 ± 3.73
UW/ NW/ OW/ OB (*n*)	24/ 357/ 111/ 37	10/ 181/ 54/ 22	14/ 176/ 57/ 15
UW/ NW/ OW/ OB (%)	4.5%/ 67.5%/ 21%/ 7%	3.7% / 67.8%/ 20.3%/ 8.2%	5.3%/ 67.2%/ 21.8%/ 5.7%
BF%	20.7 ± 8.3	25.4 ± 7.0	15.9 ± 6.7*
WC (cm)	73.1 ± 10.2	72 ± 10.2	74.2 ± 10.2*
WHtR	0.45 ± 0.06	0.45 ± 0.6	0.46 ± 0.6
WsHtR	0.86 ± 0.11	0.86 ± 0.12	0.87 ± 0.1
CRP (mg/L)	0.95 ± 1.88	0.77 ± 1.59	1.13 ± 2.12*
Fibrinogen (mg/dL)	264 ± 43.2	268.13 ± 41.72	259.77 ± 44.43*
Adiponectin (mg/L)	11.61 ± 5.45	12.90 ± 5.74	10.29 ± 4.79*
Complement C3 (g/L)	1.17 ± 0.16	1.18 ± 0.16	1.17 ± 0.16
Complement C4 (g/L)	0.21 ± 0.06	0.21 ± 0.06	0.21 ± 0.06
ESR (mm/hour)	6.22 ± 6.15	7.44 ± 6.47	4.98 ± 5.53*
Leptin (ng/mL)	4.12 ± 4.93	6.21 ± 5.6	1.98 ± 2.85*
	n (%)	*n* (%)	*n* (%)
Tanner A			
Stage ≤2	41 (7.8)	8 (3.0)	33 (12.6)
Stage 3	171 (32.3)	78 (29.2)	93 (35.5)
Stage 4	247 (46.7)	145 (54.3)	102 (38.9)
Stage 5	70 (13.2)	36 (13.5)	34 (13.0)
Tanner B			
Stage ≤2	37 (7.0)	6 (2.2)	31 (11.8)
Stage 3	115 (21.7)	64 (24.0)	51 (19.5)
Stage 4	262 (49.5)	125 (46.8)	137 (52.3)
Stage 5	115 (21.8)	72 (27.0)	43 (16.4)

$p < 0.05$ for sex comparisons (two-tailed *t*-test).

BF%, body fat percentage; BMI, body mass index (according to the age and sex-specific cut-off values of the International Obesity Task Force [IOTF]); CRP, high sensivity C-reactive protein; ESR, erythrocyte sedimentation rate; NW, normal weight; OB, obese; OW, overweight; SD, standard deviation; Tanner A, breast development in girls, genital development in boys; Tanner B, pubic hair development; UW, underweight; WC, waist circumference; WHtR, waist-to-height ratio; WsHtR, waist-to-sitting-height ratio.

the drop of the expression of these adipokines;[32] boys from our study were mainly in pubertal stages 4 and 5.

BMI also presented a slightly higher AUC than BF% predicting CRP, but this time in girls. Analysis of the data from the National Health and Nutrition Examination Survey (NHANES)[3,33,34] suggests that BMI is a good predictor of elevated CRP in children, and has been widely used to predict body composition and health-related risks.[9,10] Indeed, in a recent systematic review and meta-analysis[35] the random-effects summary correlation between BMI and CRP in children and adolescents was strong (r = 0.37; 95% CI = 0.31–0.43).

Nevertheless, it is important to emphasize that BMI is a measure of excess weight relative to height and does not provide information on the distribution of body fat, nor does it differentiate between fat and lean mass.[36] In this

Table 2. AUC, 95% CI, *P* Values, Sensitivity, Specificity, and Cut-Off Values for the Associations of Measures of Overall and Abdominal Adiposity with Inflammatory and Metabolic Markers for Girls

			CRP	Fibrinogen	ESR	C3	C4	Adiponectin	Leptin
Measures of overall adiposity	BMI (kg/m²)	AUC	**0.754**[a]	0.641	0.588	0.708	0.660	0.662	**0.913**
		95% CI	**0.698–0.804**	0.580–0.698	0.526–0.648	0.649–0.762	0.600–0.716	0.602–0.718	**0.872–0.944**
		p value	**<0.001**	0.004	0.101	<0.001	0.004	0.004	**<0.001**
		Sensitivity	**88.0**	74.4	94.3	66.7	87.5	46.7	**96.8**
		Specificity	**57.4**	51.8	26.3	70.2	45.1	89.9	**71.6**
		Cut-off	≥**21.18**	≥20.65	≥18.40	≥22.43	≥19.88	≥25.17	≥**22.35**
	BF%	AUC	0.748	**0.660**	**0.625**	**0.720**	**0.677**	**0.672**	0.908
		95% CI	0.692–0.799	**0.600–0.717**	**0.564–0.683**	**0.662–0.773**	**0.617–0.732**	**0.612–0.728**	0.866–0.940
		p value	<0.001	**<0.001**	**0.019**	**<0.001**	**0.001**	**0.002**	<0.001
		Sensitivity	92.0	**62.8**	**94.3**	**51.3**	**81.2**	**56.7**	87.1
		Specificity	51.7	**67.4**	**28.0**	**85.1**	**54.0**	**79.7**	80.1
		Cut-off	≥24.40	≥**27.31**	≥**20.32**	≥**30.7**	≥**24.71**	≥**29.9**	≥29.40
Measures of abdominal adiposity	WC (cm)	AUC	0.716	0.658	0.602	0.698	**0.634**	0.663	0.872
		95% CI	0.657–0.769	0.598–0.715	0.540–0.661	0.639–0.753	**0.573–0.691**	0.603–0.720	0.826–0.910
		p value	<0.001	0.001	0.057	<0.001	**0.016**	0.004	<0.001
		Sensitivity	68.0	41.9	82.9	51.3	**90.6**	50.0	87.1
		Specificity	74.4	83.9	34.5	85.1	**35.3**	83.1	75.4
		Cut-off	≥75.1	≥77.6	≥67.0	≥77.6	≥**67.0**	≥77.5	≥74.5
	WHtR	AUC	**0.757**	**0.666**	0.598	0.700	0.619	**0.700**	**0.880**
		95% CI	**0.701–0.807**	**0.606–0.722**	0.536–0.657	0.641–0.754	0.558–0.678	**0.641–0.754**	**0.835–0.916**
		p value	**<0.001**	**<0.001**	0.068	<0.001	0.033	**<0.001**	**<0.001**
		Sensitivity	**84.0**	**72.1**	45.7	56.4	68.7	**60.0**	**93.5**
		Specificity	**65.3**	**56.7**	73.7	80.3	52.3	**78.1**	**67.8**
		Cut-off	≥**0.46**	≥**0.45**	≥0.48	≥0.48	≥0.44	≥**0.48**	≥**0.46**
	WsHtR	AUC	0.748	0.663	0.604	**0.710**	0.616	0.675	0.850
		95% CI	0.691–0.799	0.603–720	0.499–0.622	**0.651–0.763**	0.555–0.675	0.616–0.731	0.801–0.891
		p value	<0.001	<0.001	0.051	**<0.001**	0.037	0.002	<0.001
		Sensitivity	76.0	76.7	51.4	**66.7**	50.0	53.3	64.5
		Specificity	74.0	50.4	73.3	**76.3**	71.9	80.6	90.3
		Cut-off	≥0.88	≥0.83	≥0.89	≥**0.89**	≥0.88	≥0.92	≥0.97

AUC, area under the curve; CI, confidence interval, BF%, body fat percentage; BMI, body mass index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; WC, waist circumference; WHtR, waist-to-height ratio; WsHtR, waist-to-sitting-height ratio.

[a]Values in bold represent the ROC curves indicating the adiposity measures that presented the higher AUC for each biomarker.

study we could observe that for a similar BMI value for age, girls and boys are different in relation to body composition, indicated by a significant higher BF% in girls. In a 7.5-year longitudinal study, Wen et al.[6] showed that increases in fat mass explained the increases in CRP levels during pubertal growth of Finnish girls but not vice versa.

BF% was the only adiposity measure that showed discriminatory power for all the biomarkers in girls. But it should also be noted that—albeit BMI has presented marginally inferior AUC than BF% for the rest of the biomarkers (except for CRP in girls and leptin for both sexes)—BMI still showed discriminatory power for most

Table 3. AUC, 95% CI, *P* Values, Sensitivity, Specificity, and Cut-Off Values for the Associations of Measures of Overall and Abdominal Adiposity with Inflammatory and Metabolic Markers for Boys

			CRP	Fibrinogen	ESR	C3	C4	Adiponectin	Leptin
Measures of overall adiposity	BMI (kg/m^2)	AUC	0.590	0.608	0.534	0.688	0.565	0.560	**0.929**[a]
		95% CI	0.527–0.650	0.546–0.668	0.472–0.596	0.628–0.743	0.502–0.626	0.498–0.621	**0.890–0.957**
		p value	0.15	0.029	0.587	<0.001	0.21	0.29	**<0.001**
		Sensitivity	76.0	73.8	83.3	48.9	70.3	26.7	**97.1**
		Specificity	48.1	46.8	39.1	82.9	48.9	95.3	**79.8**
		Cut-off	≥20.23	≥20.07	≥19.60	≥23.37	≥20.23	≥27.57	≥**22.34**
	BF%	AUC	0.558	**0.613**	0.574	**0.689**	0.566	0.600	0.911
		95% CI	0.496–0.619	**0.551–0.673**	0.511–0.634	**0.629–0.745**	0.504–0.627	0.538–0.660	0.869–0.942
		p value	0.349	**0.022**	0.246	**<0.001**	0.20	0.08	<0.001
		Sensitivity	24.0	**50.0**	58.3	**60.0**	27.0	46.7	91.2
		Specificity	94.5	**71.8**	61.3	**73.7**	94.2	78.0	84.2
		Cut-off	≥26.2	≥**18.3**	≥16.4	≥**18.2**	≥25.8	≥20.2	≥20.1
Measures of abdominal adiposity	WC (cm)	AUC	**0.630**	**0.629**	0.544	**0.693**	0.584	0.593	0.900
		95% CI	**0.568–0.688**	**0.568–0.688**	0.482–0.606	**0.634–0.749**	0.521–0.644	0.530–0.653	0.858–0.934
		p value	**0.038**	**0.009**	0.482	**<0.001**	0.11	0.10	<0.001
		Sensitivity	**64.0**	**57.1**	75.0	**44.4**	32.4	40.0	91.2
		Specificity	**60.3**	**63.2**	39.5	**87.1**	83.1	83.6	77.6
		Cut-off	≥**74.2**	≥**74.6**	≥70.0	≥**82.5**	≥82	≥82	≥76.5
	WHtR	AUC	0.604	0.592	0.546	0.689	0.554	0.587	**0.911**
		95% CI	0.542–0.664	0.530–0.652	0.484–0.607	0.629–0.744	0.492–0.615	0.525–0.648	**0.870–0.943**
		p value	0.095	0.062	0.465	<0.001	0.30	0.129	**<0.001**
		Sensitivity	52.0	33.3	45.8	48.9	29.7	36.7	**91.2**
		Specificity	66.7	87.3	66.0	82.9	92.4	89.2	**80.7**
		Cut-off	≥0.47	≥0.51	≥0.47	≥0.49	≥0.54	≥0.52	≥**0.48**
	WsHtR	AUC	0.603	0.624	0.561	0.691	0.567	0.608	0.896
		95% CI	0.541–0.663	0.563–0.683	0.543–0.663	0.631–0.746	0.503–0.627	0.547–0.668	0.853–0.931
		p value	0.09	0.012	0.33	<0.001	0.20	0.059	<0.001
		Sensitivity	44.0	66.7	83.3	46.7	27.0	36.7	88.2
		Specificity	75.5	59.1	34.5	87.1	94.6	86.6	82.0
		Cut-off	≥0.92	≥0.86	≥0.81	≥0.95	≥1.04	≥0.96	≥0.92

AUC, area under the curve; BF%, body fat percentage; BMI, body mass index; CI, confidence interval, CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; WC, waist circumference; WHtR, waist-to-height ratio; WsHtR, waist-to-sitting-height ratio.

[a]Values in bold represent the ROC curves indicating the adiposity measures that presented the higher AUC for each biomarker.

biomarkers, and these differences from BF% were not statistically significant.

Concerning the predictive power of the measures of abdominal adiposity, we observed different trends. In girls, WHtR presented the highest AUC for most of the biomarkers, while for boys WC was the measure that more often provided better discriminatory power. We chose to include and test WsHtR due to its novel character and potential usefulness for screening obesity and related health risks,[37] but it only presented the higher AUC when compared with the other abdominal adiposity measures for C3, in girls.

Some authors[38,39] argue that measures of abdominal adiposity might be more useful predictors of cardiometabolic risk in nonobese adolescents, once excess abdominal adiposity could be missed if using a whole body measure such as BMI. There may also exist differences between sexes, as Cartier et al.[40] highlighted; although in adults, CRP concentrations seem to be influenced to a greater extent by visceral adiposity in men, as opposed to subcutaneous adiposity in women.

In a study with healthy Spanish adolescents,[41] the authors showed that although BMI and WC are strongly correlated and that both measures were good predictors of fat content in children and adolescents, they also report that different biomarkers associated with different adiposity measures. In that study, C3, unlike CRP, C4, and ceruloplasmin, was preferentially associated with WC compared to BMI in both sexes after further adjustments for age and pubertal maturity.

In another study, composed exclusively by German male adolescents,[42] WHtR presented a higher AUC for CRP than WC and WHR. In our study, WC was the measure of central adiposity that provided better discriminatory power for detecting CRP in boys. We observed similar results to Jung et al.[42] only in girls.

According to Taylor et al.,[39] youths have the WC equivalent of adult abdominal obesity at percentiles lower than the frequently used pediatric threshold of 90%. Besides, the WC cut-off values for pediatric ages have to be age- and sex specific, so a fixed cut-off point for WC not taking account of height might underestimate the relative amount of abdominal fat in short subjects and overestimate it in tall subjects. Likewise, some authors[43–45] adjusted the WC to the person's height, proposing the WHtR as a way of assessing shape and monitoring risk reduction, first in adults, suggesting that values >0.5 were indicative of increased health risks for both sexes, and then in youth as young as five years old,[46–48] making it interestingly age and sex independent. Systematic reviews and meta-analysis[49–51] have been suggesting some superiority of WHtR over WC and BMI for detecting cardiometabolic risk factors in adults and children of both sexes, of various nationalities and ethnic groups.

In our study, although boys had higher values of WC, it probably does not reflect larger intra-abdominal fat depots, because when the height of the subjects is considered, we observe that they are also significantly taller than girls, in a proportion that seems to correct this apparent abdominal obesity in boys. Indeed, there were no differences between sexes in the mean values of WHtR and WsHtR. In addition, the mean values of WC of the participants of both sexes are placed between the 50th and the 75th percentiles of Portuguese adolescents' reference data.[52]

The cut-off points range for WHtR suggested by the ROC analysis in our study to predict increased levels of inflammatory markers in girls (0.44–0.48) and in boys (0.48–0.49) are slightly below the international proposed cut-off value of ≥0.5 that is frequently associated with greater risks of overweight and metabolic syndrome, suggesting that even slightly below this threshold, some adolescents could present increased levels of some biomarkers. These are in line with other studies[53,54] suggesting that a WHtR <0.5 could predict adverse outcomes in youths. Nevertheless, further research on this topic in pediatric ages is needed to confirm or contrast our findings.

The present study is not without limitations. First, its cross-sectional design does not allow us to assess the directionality of the relationships between the different adiposity measures and the different biomarkers. Second, the use of a single measure of each biomarker may not accurately reflect a long-term inflammatory pattern of that specific biomarker. Last, our sample is not nationally representative, and therefore these results cannot be extended to the entire population of Portuguese adolescents.

The strengths of this study include the analysis of various biomarkers, which provided us with a more accurate assessment of the inflammatory status of the adolescents, since we rely not only on a single marker; and the utilization of various simple, inexpensive, and widespread measures of adiposity. The associations between those measures and several biomarkers should be further explored in the future, as they could be seen as indirect indicators of the inflammation profile of a sample of adolescents, particularly in epidemiological studies, when a large number of individuals are assessed and when blood samples may not be taken.

In conclusion, our results highlight the ability and utility of several anthropometric measures of overall and abdominal adiposity in detecting increased levels of biomarkers in adolescents. The measures that more often presented discriminatory power were, for overall adiposity, BF% for both sexes, and in relation to abdominal adiposity, WHtR in girls and WC in boys. However, the small differences in discriminatory capabilities between adiposity measures are perhaps of limited relevance. Based on our data it is difficult to clearly defend the adoption of a single measure of obesity in preference to all others.

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Artigo Original III

Associations Between Early Life Anthropometric Indicators and Low-Grade Inflammation, Insulin Resistance and Lipid Profile During Adolescence: the LabMed Physical Activity Study

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ABSTRACT

Introduction: Overweight and obesity have been associated to unfavourable health-related outcomes. However, the long-term relations between excessive adiposity in early childhood and unfavourable cardiometabolic profiles in adolescence and adulthood are not yet completely understood. We aimed to assess the associations between early life anthropometric indicators, such as birth weight (BW) or BMI at several time points of age (6,12 and 18 months, and at 2,3, 4, 5 and 6 years old), and low-grade inflammation, insulin resistance and lipid profiles later in adolescence.

Methods: Retrospective school-based study with 415 Portuguese adolescents (220 girls, 195 boys) with a mean age of 14.08±1.6 years old. Anthropometric data from birth to the age of 6 years was extracted from individual child health book records. Actual weight and height were measured, and BMI was calculated. Participants were classified at each time point as normal weight or overweight according to WHO reference values. C-reactive protein, fibrinogen, erythrocyte sedimentation rate, complements C3 and C4, leptin, adiponectin, Interleukin-6, white blood cells, glucose, insulin, total cholesterol, LDL, HDL and triglycerides were obtained from venous blood samples. HOMA-IR and total cholesterol/HDL ratio were computed. Linear regressions were used to explore the associations between early life anthropometric indicators and inflammatory, insulin resistance and lipid profiles in adolescence.

Results: From the age of 2 years onwards, BMI was positively associated with the inflammatory score and HOMA-IR in adolescence, after adjustments for age, pubertal stage, BMI, body fat percentage, socioeconomic status and KIDMED index. When compared to their normal weight counterparts, overweight or obese children at the ages of 2, 3, 4, 5, and 6 years, presented a significantly higher inflammatory score and HOMA-IR index later in adolescence. TC/HDL ratio was also positively associated with BMI, but only from the age of 5 years onwards. The associations between BMI and cardiometabolic outcomes remained positive in adolescence, with the overweight adolescents presenting a higher inflammatory score, HOMA-IR and TC/HDL than normal weight adolescents.

Conclusion: The maintenance of a high BMI from an early age was consistently associated with worse inflammatory and lipid profiles and insulin resistance in adolescence. No associations were found between BW and the same studied outcomes.

KEYWORDS: Early life anthropometry, cardiometabolic biomarkers, overweight, adolescents.

INTRODUCTION

Overweight and obesity are considered important risk factors in the development of a series of cardiometabolic diseases (Heymsfield & Wadden, 2017), which largely remain asymptomatic during youth. These risks usually manifest themselves in adulthood, yet may originate during infancy (Berenson et al., 1998; Juonala et al., 2011; Twig et al., 2016). Higher levels of lipids and lipoproteins have been described in overweight or obese children and adolescents (Daniels & Greer, 2008; Giordano et al., 2011), and previous data from the Bogalusa study (Berenson et al., 1998) have shown that elevations of concentrations of total cholesterol (TC), low-density lipoprotein cholesterol (LDL), and triglycerides, as well as lower concentrations of high-density lipoprotein cholesterol (HDL), measured in childhood, have been significantly associated with later high prevalence (≈70%) of atherosclerotic lesions in young adulthood.

In addition to an unfavourable lipid profile (Daniels & Greer, 2008), overweight and obese subjects usually also present impaired glucose metabolism (D'Adamo & Caprio, 2011) and higher levels of several inflammatory biomarkers (DeBoer, 2013) than their normal weight counterparts. Although C-reactive protein (CRP) has been the most used marker of inflammation, other biomarkers such as the acute phase reactants fibrinogen and complement factors C3 (C3) and C4 (C4), cytokines as interleukin-6 (IL-6), adipokines as leptin and adiponectin, and non-specific systemic markers of inflammation such as erythrocyte sedimentation rate (ESR) and white blood cells (WBC), have been explored as useful for assessing risk of cardiovascular diseases, and to more accurately characterize the low-grade inflammatory profile of an individual (Balagopal et al., 2011; Calder et al., 2013; Pearson et al., 2003). Further, these measures are valid in adults, children and adolescents (Artero et al., 2014; Cohen et al., 2012; Guran et al., 2007; Labayen et al., 2009; Martinez-Gomez et al., 2011).

The long-term maintenance of increased levels of some biomarkers in overweight and obese individuals reflect a state of chronic and systemic low-

grade inflammation, which seems to be a key component in the pathogenesis of insulin resistance and type 2 diabetes (Calder et al., 2013; Esser et al., 2014). Insulin resistance is the best predictor of diabetes, and occurs several years before the onset of the disease (D'Adamo & Caprio, 2011), making early identification important for prevention and management of the disease. The homeostatic model assessment of insulin resistance (HOMA-IR) (Matthews et al., 1985) is used as a valid measure of insulin resistance in non-diabetic children and adolescents (Gungor et al., 2004), and has been reported as being substantially increased in overweight/obese children compared with normal-weight (Lee et al., 2006).

Birth weight (BW) is commonly used as a proxy measure of intrauterine development, and both low and high BW have been explored as determinants for impaired future health related-outcomes, such as type 2 diabetes and the metabolic syndrome later in life (Johnsson et al., 2015; Vaag, 2009). However, others studies suggest that growth patterns in infancy and childhood might have a more pronounced effect than with BW *per se* (Baker et al., 2007; Leunissen et al., 2009).

Since there is strong evidence that overweight and obesity tracks from early childhood to adolescence and adulthood (Evensen et al., 2016), and that body mass index (BMI) is the most commonly used anthropometric index to define weight status in large samples (Cole et al., 2000; WHO, 2000), its close monitoring throughout early life could represent not only a procedure to identify an overweight condition, but also an easy but useful way to prevent and detect a series of health-related parameters/diseases associated with that condition, such as diabetes and cardiovascular diseases.

Although cross-sectional studies have consistently associated overweight with inflammatory and cardiometabolic biomarkers, to the best of our knowledge, those relations are not yet clear in the long-term. Further, it is not well established that a persistently high BMI during infancy and childhood can predict an unfavourable state of biomarkers, in adolescence. Thus, the main objective of this study was to assess the associations between early life

anthropometric indicators such as birth weight or BMI at several time points of age (6,12 and 18 months, and at 2, 3, 4, 5 and 6 years), with indicators of inflammation, insulin resistance and lipid profile during adolescence.

SUBJECTS, MATERIALS AND METHODS

Study design and sampling

This study is based on data from the Longitudinal Analysis of Biomarkers and Environmental Determinants of Physical Activity Study (LabMed Physical Activity Study), a 3-year longitudinal cohort study started during the fall of 2011, and carried out in five schools in the north of Portugal, with the main aim of assessing the independent and combined associations of dietary intake and fitness levels on blood pressure levels of adolescents. The study protocol and procedures are described in detail elsewhere (Oliveira-Santos et al., 2016). Briefly, from an initial sample of 1229 apparently healthy adolescents (12–18 years old) that agreed to participate in that study, 534 provided blood samples. Subsequently, 5 individuals were excluded due to high-sensitivity CRP values >10 mg/L, which were indicative of acute inflammation or illness (Ridker, 2003). Child Health Booklets records of 539 participants were also available for complete early life data extraction. In total, 415 adolescents matched information from early life and blood variables, and, as such, composed the final sample for the present study.

This study was conducted in accordance to the Helsinki Declaration for Human Studies of 1975, as revised in 2013 (World Medical Association, 2013), and approved by the Portuguese Data Protection Authority (#1112434/2011) and the Portuguese Ministry of Science and Education (0246200001/2011). All participants were previously informed of this study aims, and written informed consent was obtained from participating adolescents and their parents/tutors.

Early life data collection

Information on birth and postnatal periods was retrospectively collected from individual child health booklets records provided by the participants, called *Boletim de Saúde Infantil e Juvenil*. Anthropometric data regarding weight, length and height measurements, available from birth up until the age of 6 years, which were performed and recorded on the health booklets by the paediatricians during regular appointments with the participants, were extracted for the present analysis. Subjects were considered born with low BW (<2500g), adequate BW (2500–4000g), or high BW (>4000g), according WHO references (WHO & UNICEF, 2004). BMI was calculated as weight divided by length squared (kg/m^2) from birth up until the age of 2 years, and from 2 years onward calculated as usual (weight divided by squared height [kg/m^2]). At the ages of 6, 12 and 18 months, and at 2, 3, 4, 5 and 6 years, the participants were classified according the BMI-for-age percentiles sex specific references provided by the World health Organization (WHO, 2007, 2006), in one of two possible categories: normal weight (including underweight individuals) or overweight (including obese participants).

Anthropometric measurements in adolescence

Anthropometric measures such as weight and height were collected according standardized procedures (Lohman et al., 1988) and described elsewhere (Oliveira-Santos et al., 2016). BMI was then calculated as previously described (kg/m^2), and all the adolescents were classified in two categories, normal weight (including underweight) or overweight (including obese), using the age and sex-specific BMI-for-age percentiles cut-off values proposed by the World Health Organization (WHO, 2007).

Body fat percentage (BF%) was estimated by bioelectrical impedance (Tanita Inner Scan BC 532, Tokyo, Japan) according to manufacturer's instructions. Participants were asked to fast overnight, not to drink any fluid four hours prior to their test, urinate within 30 min of test and not to perform any physical exercise in that morning, in order to minimize eventual errors and

variations in the BF% assessment measurements (Dixon et al., 2013; Goss et al., 2003).

Pubertal stage assessment

Pubertal stages of sexual maturation (A - breast development in girls; genital development in boys; and B – pubic hair development, for both sexes) were self-assessed by the participants according to the classification by Tanner (1962), in a private place, and then communicated in a closed envelope to a researcher of the same sex, with stage 1 being pre-pubertal, and 5 being adult maturation. Given the low number of subjects at Tanner stage 1, these were integrated with Tanner stage 2 and formed the pre-pubertal group.

Biochemical assessment

Blood samples were collected by venepuncture from the antecubital vein from each subject early in the morning, following a 10-hour overnight fast. The samples were stored in sterile blood collection tubes in refrigerated conditions (4° to 8°C) for no longer than 4 hours, during the morning of collection, and then delivered to an analytical laboratory for testing for a series of inflammatory markers, lipid profile (total cholesterol and fractions, triglycerides), and glucose and insulin determinations, according to standardized procedures, as follows: (i) high-sensitivity CRP, latex enhanced immunoturbidimetric assay (Siemens ADVIA 1800, Erlangen, Germany); (ii) fibrinogen, Clauss assay (Siemens BCS XP System, Erlangen, Germany); (iii) adiponectin and leptin, ELISA (Plate Reader); (iv) complement factor C3 and complement factor C4, PEG enhanced immunoturbidimetric assay (Siemens ADVIA 1800, Erlangen, Germany); (v) ESR, Westergren method (Starrsed, RR Mechanotronics, Netherlands); (vi) IL-6, Chemiluminescence immunoassay (Siemens Immulite 2000, Diagnostic Products Corporation, Los Angeles, CA); (vii) WBC, Cytometry (Siemens Advia 2120i); (viii) Glucose, Hexokinase method (Siemens Advia 1600/1800 Erlangen, Germany); (ix) Insulin, Chemiluminescence immunoassay (Siemens ACS Centaur System, Erlangen, Germany); (x) TC, HDL, LDL and triglycerides were

measured by standard enzymatic methods (Siemens Advia 1600/1800, Erlangen, Germany). CRP, C3, C4, IL-6, adiponectin, leptin, glucose, insulin, TC, HDL, LDL and triglycerides were determined in serum, ESR and WBC were determined in whole blood, and fibrinogen was determined in plasma.

HOMA-IR [as the product of fasting insulin (μIU/ml) and fasting glucose (mmol/l) divided by the constant 22.5] (Matthews et al., 1985) was used as a surrogate measure of insulin resistance (Gungor et al., 2004). The ratio of TC to HDL (TC/HDL) was calculated, and used in the analyses as an index of an atherogenic lipid profile, as some studies have suggested that it provides a useful summary of the joint contribution of TC and HDL to cardiovascular disease risk (Abreu et al., 2014; Lobelo et al., 2010; Millan et al., 2009).

Socioeconomic Status

The Family Affluence Scale (Currie et al., 2008) was used as a proxy measure of adolescent's socioeconomic status. This scale is a four-item questionnaire regarding information on vehicles, home, lifestyle and access to technology, with a range of scores from 0 to 9 points, that allows adolescents to indirectly report their family income, with the highest score corresponding to the highest socioeconomic level.

KIDMED index

The KIDMED index (Serra-Majem et al., 2004) (Mediterranean Diet Quality Index for children and adolescents) was used to assess the degree of adherence to the Mediterranean diet, considered a healthy dietary model and associated to a lower occurrence of cardiometabolic diseases (Ros et al., 2014) and certain cancer types (Schwingshackl & Hoffmann, 2015). This index is based on a 16 questions self-administered, which sustain principles of Mediterranean dietary patterns as well as those that undermine it. Questions indicating a negative connotation with respect to the Mediterranean diet were assigned a value of -1 and those with a positive aspect +1. The sum of the

values ranges from 0 to 12, where a higher index means good adherence to the Mediterranean diet.

Statistical analyses

Descriptive statistics are presented as means and standard deviations. Two-sided Student's t-test was used to compare groups for continuous variables and chi-square for categorical variables.

As no marker alone seems to perfectly characterize the inflammatory profile of an individual, several studies in paediatric populations have been using a combined score of inflammatory biomarkers, since this approach seems to provide a more comprehensive assessment and characterization of the inflammatory state in adolescence (Artero et al., 2014; Calder et al., 2013). For that purpose, partial correlations adjusted for age, sex, pubertal stage, BMI, BF%, adherence to a Mediterranean dietary pattern (KIDMED index) and socioeconomic status, were used as a preliminary analysis to examine the associations between each inflammatory biomarker with BW and BMI at each age point during childhood (Supplemental Table 1). Significant correlations ($p \leq 0.05$) served as the criteria used to select 6 inflammatory biomarkers (C3, C4, CRP, ESR, fibrinogen, leptin) for the construction of a continuous inflammatory score. For each biomarker, a z-score was computed by sex, age and pubertal status, and all the z-scores of the individual were then summed to create a cluster of inflammatory biomarkers. A higher score is indicative of a worse inflammatory profile.

Linear regression analyses adjusted for age, pubertal stage, BMI, BF%, socioeconomic status and KIDMED index were performed to determine the associations between the clustered inflammatory biomarkers score, HOMA-IR and TC/HDL (as dependent variables), with BW and BMI at the ages of 6, 12 and 18 months, and at 2, 3, 4, 5 and 6 years of age (as predictor variables). Unstandardized regression coefficients were used to express the beta in the linear regression analyses, and the coefficient of determination was used to assess the variance explained in the model.

Analysis of Covariance with Bonferroni post-hoc multiple comparison tests was used to assess if children that were normal weight and overweight/obese at each time point of age analysed, presented differences in inflammatory, insulin resistance and lipid profiles during adolescence. Covariates included were age, pubertal stage, BMI, BF%, socioeconomic status and KIDMED index.

Replication of all the analyses was performed without preterm deliveries (n=30, 7.2%) and twins (n=8, 1.9%), in order to reduce bias. However, as these analyses did not yield different results, we included all the 415 participants in the final analyses.

Data were analysed using the Statistical Package for Social Sciences version 24.0 (SPSS, IBM Corp., NY, USA). A *p*-value ≤0.05 was considered to denote statistical significance.

RESULTS

Tables 1 and 2 presents the descriptive characteristics of the participants at early life and adolescence periods. Boys were taller and heavier than girls, and presented significantly higher values of BW, birth length, and BMI at 6, 12 and 18 months of age ($p \leq 0.05$ for all). BF%, adiponectin, ESR, fibrinogen, leptin, insulin, HOMA-IR, TC, LDL, triglycerides and HDL values were significantly higher in girls, while fasting glucose and TC/HDL were significantly higher in boys ($p \leq 0.05$ for all).

Table 1. Characteristics of the Participants at Early Life and Adolescence Periods

	All (*n* = 415)	**Girls (*n* = 220)**	**Boys (*n* = 195)**
Variables	Mean (SD)	Mean (SD)	Mean (SD)
Age (years)	14.08 (1.64)	14.13 (1.67)	14.04 (1.62)
Height (cm)	159.2 (9.19)	157.4 (6.7)	161.4 (10.9) **
Weight (kg)	54.475 (12.741)	52.896 (10.942)	56.257 (14.326) *
BMI (kg/m^2)	21.31 (3.83)	21.29 (3.87)	21.34 (3.79)
NW (n; %)	278; 67%	156; 70.9%	122; 62.6%
OW (n; %)	137; 33%	64; 29.1%	73; 37.4%
BF (%)	21.14 (8.04)	25.26 (6.94)	16.49 (6.53) **
Birth weight (g)	3 277 (492)	3 190 (490)	3 377 (476) **
Low (n; %)	27; 6.5%	19; 8.6%	8; 4.1%
Normal (n; %)	366; 88.2%	192; 87.3%	174; 89.2%
High (n; %)	22; 5.3%	9; 4.1%	13; 6.7%
Birth length (cm)	49.1 (2.2)	48.6 (2.2)	49.7 (2.0) **
BMI at 6 months (kg/m^2)	17.41 (1.54)	17.08 (1.37)	17.81 (1.63) **
BMI at 12 months (kg/m^2)	17.73 (1.54)	17.35 (1.42)	18.13 (1.57) **
BMI at 18 months (kg/m^2)	17.19 (1.43)	16.95 (1.35)	17.45 (1.48) *
BMI at 2 years (kg/m^2)	16.82 (1.47)	16.67 (1.38)	16.98 (1.56)
BMI at 3 years (kg/m^2)	16.56 (1.70)	16.42 (1.75)	16.72 (1.63)
BMI at 4 years (kg/m^2)	16.62 (1.90)	16.52 (1.93)	16.73 (1.87)
BMI at 5 years (kg/m^2)	16.86 (2.20)	16.78 (2.25)	16.94 (2.16)
BMI at 6 years (kg/m^2)	17.19 (2.61)	16.96 (2.54)	17.46 (2.68)
Pubertal stage A (%)			
Stage ≤ II	8.4	3.6	13.8
Stage III	34.2	31.4	37.4
Stage IV	43.9	52.3	34.4
Stage V	13.5	12.7	14.4
Pubertal stage B (%)			
Stage ≤ II	7.7	2.7	13.3
Stage III	23.9	25.5	22.1
Stage IV	46.7	44.1	49.7
Stage V	21.7	27.7	14.9
KIDMED index	7.16 (2.06)	7.29 (2.03)	7.02 (2.10)
Socioeconomic status (FAS)	6.50 (1.66)	6.56 (1.65)	6.42 (1.65)

$^*p < 0.05$; $^{**}p < 0.001$ for sex comparisons (two-tailed *t*-tests for continuous variables or chi-square for categorical variables).

Abbreviations: BF (%), body fat percentage; BMI, body mass index; FAS, family affluence scale; NW, underweight + normal weight; OW, overweight + obese; SD, standard deviation; Pubertal stages of sexual maturation (A - breast development in girls; genital development in boys; and B – pubic hair development, for both sexes);

Table 2. Biochemical Characteristics of the Adolescents

	All (*n* = 415)	**Girls (*n* = 220)**	**Boys (*n* = 195)**
Variables	Mean (SD)	Mean (SD)	Mean (SD)
Adiponectin (mg/L)	11.99 (5.56)	13.19 (5.98)	10.65 (4.69) **
C-reactive protein (mg/L)	0.87 (1.69)	0.74 (1.61)	1.00 (1.78)
Complement C3 (mg/dL)	118.38 (16.14)	118.70 (16.19)	118.03 (16.12)
Complement C4 (mg/dL)	21.13 (6.39)	21.35 (6.58)	20.89 (6.18)
Erythrocyte sedimentation rate (mm/h)	6.49 (6.58)	7.61 (6.87)	5.25 (6.01) **
Fibrinogen (mg/dL)	265.42 (43.31)	269.52 (43.13)	260.78 (43.15) *
IL-6 (ng/L)	3.76 (4.78)	3.70 (4.27)	3.82 (5.31)
Leptin (ng/ml)	4.28 (4.99)	6.18 (5.58)	2.13 (3.07) **
White blood cells (10^9/L)	7.14 (1.65)	7.26 (1.62)	7.01 (1.66)
Fasting glucose (mmol/L)	4.90 (0.40)	4.84 (0.42)	4.97 (0.37) *
Insulin (μU/ml)	14.79 (7.56)	16.04 (7.42)	13.37 (7.49) **
HOMA-IR	3.26 (1.77)	3.51 (1.77)	2.98 (1.74) *
Total cholesterol (mg/dL)	154.14 (28.13)	159.37 (28.62)	148.25 (26.42) **
LDL (mg/dL)	85.09 (23.64)	87.79 (24.30)	82.05 (22.54) *
HDL (mg/dL)	54.87 (12.05)	57.90 (12.29)	51.46 (10.82) **
Triglycerides (mg/dL)	67.92 (32.19)	70.85 (32.62)	64.61 (31.47) *
TC/HDL ratio (mg/dL)	2.89 (0.61)	2.83 (0.59)	2.96 (0.62) *

$^{*}p \leq 0.05$; $^{**}p < 0.001$ for sex comparisons (two-tailed *t*-test)

Abbreviations: HOMA-IR, Homeostatic model assessment of insulin resistance index; IL-6, Interleukin 6; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; SD, standard deviation; TC/HDL ratio, total cholesterol/high-density lipoprotein cholesterol ratio

Regression analyses in Tables 3 and 4 showed that, for both sexes, from the age of 2 years onwards BMI was significantly and positively associated with the inflammatory score and HOMA-IR in adolescence, after adjustments for age, pubertal stage, BMI, BF%, socioeconomic status and KIDMED index. TC/HDL ratio at adolescence was also positively associated with BMI, but only at the ages of 5 and 6 years. BMI in adolescence remained positively associated with the inflammatory score, HOMA-IR and TC/HDL.

Table 3. Linear Regression Coefficients, Significance Values and Coefficients of Determination, Examining the Associations Between Birth Weight and BMI at Several Time Points of Age, and Inflammatory Score, HOMA-IR and TC/HDL Ratio of Adolescent Girls, Adjusted for Age, Pubertal Stage, BMI, BF%, Socioeconomic Status and KIDMED Index

		Dependent Variables		
		Inflammatory Score	**HOMA–IR**	**TC/HDL**
Birth weight	B (*p* value)	0.000 (0.708)	0.000 (0.097)	-4.900 (0.951)
	r^2	-0.000	0.101	0.048
BMI at 6 months	B (*p* value)	0.512 (0.280)	0.092 (0.345)	-0.017 (0.576)
	r^2	0.027	0.070	0.056
BMI at 12 months	B (*p* value)	0.510 (0.480)	0.094 (0.415)	-0.013 (0.706)
	r^2	0.024	0.081	0.004
BMI at 18 months	B (*p* value)	0.564 (0.150)	0.142 (0.122)	-0.009 (0.781)
	r^2	0.023	0.085	0.050
BMI at 2 years	B (*p* value)	**0.816 (0.001)**	**0.207 (0.022)**	0.050 (0.120)
	r^2	**0.058**	**0.124**	0.024
BMI at 3 years	B (*p* value)	**0.794 (<0.001)**	**0.228 (0.002)**	0.069 (0.090)
	r^2	**0.094**	**0.176**	0.071
BMI at 4 years	B (*p* value)	**0.928 (<0.001)**	**0.208 (0.008)**	0.025 (0.342)
	r^2	**0.151**	**0.161**	0.004
BMI at 5 years	B (*p* value)	**0.916 (<0.001)**	**0.352 (<0.001)**	**0.068 (0.003)**
	r^2	**0.215**	**0.232**	**0.131**
BMI at 6 years	B (*p* value)	**0.773 (<0.001)**	**0.165 (0.005)**	**0.041 (0.030)**
	r^2	**0.188**	**0.138**	**0.058**
Current BMI	B (*p* value)	**0.508 (<0.001)**	**0.150 (<0.001)**	**0.038 (<0.001)**
	r^2	**0.217**	**0.154**	**0.106**

Abbreviations: BMI, body mass index; B, linear regression coefficient; *p*, significance value; r^2, coefficient of determination; HOMA–IR, homeostatic model assessment of insulin resistance index; TC/HDL, total cholesterol to high-density lipoprotein cholesterol ratio.

Table 4. Linear Regression Coefficients, Significance Values and Coefficients of Determination, Examining the Associations Between Birth Weight and BMI at Several Time Points of Age, and Inflammatory Score, HOMA-IR and TC/HDL Ratio of adolescent boys, Adjusted for Age, Pubertal Stage, BMI, BF%, Socioeconomic Status and KIDMED Index

		Dependent Variables		
		Inflammatory Score	**HOMA–IR**	**TC/HDL**
Birth weight	B (*p* value)	1.370 (0.982)	-3.727 (0.887)	-6.874 (0.466)
	r^2	0.000	0.010	0.003
BMI at 6 months	B (*p* value)	-0.192 (0.356)	0.022 (0.819)	0.024 (0.451)
	r^2	0.064	0.025	0.006
BMI at 12 months	B (*p* value)	-0.012 (0.958)	0.086 (0.438)	0.021 (0.584)
	r^2	0.117	0.020	0.019
BMI at 18 months	B (*p* value)	-0.015 (0.945)	0.187 (0.054)	-0.009 (0.783)
	r^2	0.061	0.025	0.003
BMI at 2 years	B (*p* value)	**0.041 (0.012)**	**0.155 (0.020)**	0.033 (0.309)
	r^2	**0.028**	**0.071**	0.017
BMI at 3 years	B (*p* value)	**0.150 (0.046)**	**0.202 (0.025)**	0.029 (0.378)
	r^2	**0.048**	**0.036**	0.14
BMI at 4 years	B (*p* value)	**0.328 (<0.001)**	**0.274 (0.001)**	0.049 (0.096)
	r^2	**0.109**	**0.074**	0.027
BMI at 5 years	B (*p* value)	**0.285 (0.008)**	**0.225 (0.001)**	**0.042 (0.002)**
	r^2	**0.106**	**0.077**	**0.034**
BMI at 6 years	B (*p* value)	**0.356 (0.016)**	**0.324 (<0.001)**	**0.046 (0.003)**
	r^2	**0.098**	**0.247**	**0.032**
Current BMI	B (*p* value)	**0.439 (<0.001)**	**0.225 (<0.001)**	**0.044 (<0.001)**
	r^2	**0.167**	**0.241**	**0.069**

Abbreviations: BMI, body mass index; B, linear regression coefficient; *p*, significance value; r^2, coefficient of determination; HOMA–IR, homeostatic model assessment of insulin resistance index; TC/HDL, total cholesterol to high-density lipoprotein cholesterol ratio.

ANCOVA adjusted for age, pubertal stage, BMI, BF%, socioeconomic status and KIDMED index confirmed the results of the linear regressions, as can be seen in Tables 5 and 6. When compared to normal weight, overweight children at the ages of 2, 3, 4, 5, and 6 years, presented a significantly higher inflammatory score and HOMA-IR later in adolescence ($p \leq 0.05$). From the age of 5, those who were overweight also presented a higher TC/HDL ratio. In adolescence, obese individuals also had higher inflammatory score, HOMA-IR and TC/HDL ratio than their normal weight counterparts.

Table 5. Analyses of Covariance of Values of the Inflammatory Score, HOMA-IR and TC/HDL Ratio of Adolescent Girls, Accordingly Their Birth Weight Category and BMI Status at Several Time Points of Age, Adjusted for Age, Pubertal Stage, BMI, BF%, Socioeconomic Status and KIDMED Index

		Inflammatory Score		HOMA–IR		TC/HDL	
		Mean (SE)		Mean (SE)		Mean (SE)	
Birth weight	LOW (8.6%)	-0.489 (0.977)		3.534 (0.385)		2.820 (0.132)	
	NORMAL (87.3%)	0.108 (0.307)		3.455 (0.121)		2.835 (0.041)	
	HIGH (4.1%)	-1.282 (1.433)		4.531 (0.565)		2.725 (0.193)	
BMI at 6 months	NW (85.4%)	-0.147 (0.342)		3.414 (0.142)		2.821 (0.046)	
	OW (14.6%)	0.862 (0.829)		3.776 (0.344)		2.813 (0.110)	
BMI at 12 months	NW (68.7%)	-0.191 (0.439)		3.686 (0.195)		2.827 (0.060)	
	OW (31.3%)	0.418 (0.652)		3.628 (0.291)		2.768 (0.090)	
BMI at 18 months	NW (61.1%)	-0.319 (0.397)		3.340 (0.157)		2.819 (0.054)	
	OW (38.9%)	0.501 (0.498)		3.783 (0.197)		2.803 (0.067)	
BMI at 2 years	NW (55.9%)	**-0.845 (0.441)**	**	**3.201 (0.164)**	*	2.726 (0.059)	
	OW (44.1%)	**1.059 (0.494)**		**3.781 (0.184)**		2.893 (0.066)	
BMI at 3 years	NW (63.0%)	**-0.806 (0.411)**	**	**3.141 (0.160)**	**	2.781 (0.057)	
	OW (37.0%)	**1.393 (0.540)**		**3.923 (0.209)**		2.923 (0.074)	
BMI at 4 years	NW (63.6%)	**-1.051 (0.431)**	***	**3.392 (0.183)**	*	2.800 (0.061)	
	OW (36.4%)	**1.871 (0.577)**		**4.028 (0.242)**		2.904 (0.081)	
BMI at 5 years	NW (61.8%)	**-1.120 (0.456)**	***	**3.251 (0.197)**	***	**2.718 (0.062)**	**
	OW (38.2%)	**1.788 (0.577)**		**4.405 (0.251)**		**3.059 (0.079)**	
BMI at 6 years	NW (56.4%)	**-1.167 (0.479)**	***	**3.296 (0.197)**	*	**2.739 (0.063)**	*
	OW (43.6%)	**1.489 (0.541)**		**3.927 (0.225)**		**2.930 (0.072)**	
Current BMI	NW (71.5%)	**-1.046 (0.279)**	***	**3.187 (0.124)**	***	**2.772 (0.041)**	**
	OW (28.5%)	**2.628 (0.446)**		**4.337 (0.198)**		**3.012 (0.065)**	

$^{*}p \leq 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$

Abbreviations: BMI, body mass index; HOMA–IR, homeostatic model assessment of insulin resistance index; TC/HDL, total cholesterol to high-density lipoprotein cholesterol ratio. NW, normal weight; OW, overweight; SEM, standard error of the mean.

Table 6. Analyses of Covariance of Values of the Inflammatory Score, HOMA-IR and TC/HDL Ratio of Adolescent Boys, Accordingly Their Birth Weight Category and BMI Status at Several Time Points of Age, Adjusted for Age, Pubertal Stage, BMI, BF%, Socioeconomic Status and KIDMED Index

		Inflammatory Score		HOMA–IR		TC/HDL	
		Mean (SE)		Mean (SE)		Mean (SE)	
Birth weight	LOW (4.1%)	-0.275 (0.819)		3.303 (0.331)		2.910 (0.117)	
	NORMAL (89.2%)	0.103 (0.222)		3.251 (0.089)		2.898 (0.032)	
	HIGH (6.7%)	-1.371 (0.913)		3.362 (0.369)		2.733 (0.130)	
BMI at 6 months	NW (75.3%)	-0.039 (0.260)		3.201 (0.111)		2.870 (0.037)	
	OW (24.7%)	0.165 (0.543)		3.560 (0.229)		2.940 (0.076)	
BMI at 12 months	NW (54.9%)	-0.122 (0.333)		3.278 (0.150)		2.880 (0.049)	
	OW (45.1%)	0.199 (0.428)		3.495 (0.193)		2.926 (0.063)	
BMI at 18 months	NW (55.8%)	-0.112 (0.295)		3.130 (0.121)		2.904 (0.043)	
	OW (44.2%)	0.159 (0.351)		3.475 (0.145)		2.869 (0.051)	
BMI at 2 years	NW (58.8%)	**-0.568 (0.315)**	**	**3.030 (0.121)**	*	2.849 (0.045)	
	OW (41.2%)	**0.757 (0.364)**		**3.473 (0.140)**		2.926 (0.052)	
BMI at 3 years	NW (64.4%)	**-0.456 (0.297)**	*	**2.964 (0.121)**	**	2.874 (0.044)	
	OW (35.6%)	**0.807 (0.395)**		**3.628 (0.161)**		2.983 (0.058)	
BMI at 4 years	NW (60.5%)	**-0.649 (0.314)**	**	**3.019 (0.137)**	**	2.885 (0.047)	
	OW (39.5%)	**1.073 (0.405)**		**3.807 (0.175)**		2.965 (0.060)	
BMI at 5 years	NW (54.4%)	**-0.819 (0.338)**	***	**2.912 (0.140)**	***	**2.831 (0.050)**	*
	OW (45.6%)	**1.146 (0.400)**		**3.864 (0.165)**		**3.001 (0.060)**	
BMI at 6 years	NW (45.0%)	**-0.959 (0.376)**	***	**2.944 (0.152)**	***	**2.847 (0.054)**	*
	OW (55.0%)	**0.999 (0.384)**		**3.752 (0.156)**		**3.018 (0.056)**	
Current BMI	NW (67.6%)	**-1.083 (0.203)**	***	**2.860 (0.086)**	***	**2.811 (0.031)**	***
	OW (32.4%)	**2.476 (0.308)**		**4.089 (0.131)**		**3.077 (0.047)**	

*$p \leq 0.05$; **$p < 0.01$; ***$p < 0.001$

Abbreviations: BMI, body mass index; HOMA–IR, homeostatic model assessment of insulin resistance index; TC/HDL, total cholesterol to high-density lipoprotein cholesterol ratio. NW, normal weight; OW, overweight; SEM, standard error of the mean.

DISCUSSION

Our study has three main findings: (i) BW showed no associations with any of the cardiometabolic outcomes in adolescence, and there were no differences in those outcomes regardless of BW; (ii) from 2 years onwards, overweight was positively associated with higher inflammatory scores and HOMA-IR in adolescence; (iii) positive associations between BMI and TC/HDL became statistically significant from the age of 5 years.

Regardless of BW category, we observed no differences in the levels of inflammatory scores, insulin resistance, or unfavourable lipid profiles later in adolescence. Our results are in agreement with other reports (Gardner et al., 2009; Jeffery et al., 2006; Rondó et al., 2013), suggesting that BW is not as relevant as other anthropometric measures during childhood in the prediction of future cardiometabolic outcomes. Previous studies with children and adolescents have also reported no associations between BW and several inflammatory biomarkers (Cook et al., 1999, 2000; Gillum, 2003; Kim et al., 2006; Rondó et al., 2013). Labayen et al. (2009) found mixed results, reporting associations between BW and some biomarkers (C3, C4, fibrinogen), but not with CRP. Instead of an individualized analysis of each biomarker, we used an inflammatory score, as it provided a more comprehensive characterization of the inflammatory state in adolescence (Artero et al., 2014; Calder et al., 2013). In addition to low-grade inflammation, our data concurs with other studies that have reported no associations between BW and other health-related outcomes, such as insulin resistance or blood lipids in late childhood (Bekkers et al., 2011; Jeffery et al., 2006) and adolescence (Horta et al., 2009; Kim et al., 2006).

As suggested by Jeffery et al. (2006), demographic changes may be one of the reasons for the apparent decrease in the importance of BW in the development of later cardiometabolic diseases (Leunissen et al., 2009). It must be taken into account that the concept of foetal programming, and its pathophysiologic consequences later in life, emerged from the pioneer works of Barker et al. (1989) and Hales et al. (1991), which were conducted on populations born in the early 20th century, who were born and grew up in the pre–World War II period, but matured in another. Moreover, socioeconomic and health conditions were totally different from those of today.

According to World Health Organization reference values (WHO & UNICEF, 2004), 6.5% of the participants in this study had low BW (<2500g) and 5.3% high BW (>4000g). However, when the same participants were assessed during the adolescence period, one third of the sample was classified as being overweight or obese. This seems to support the need for a greater emphasis that should be given on the monitoring of BMI status and its development during

infancy and childhood, even more so because overweight and obesity appear to track throughout life from early ages (de Kroon et al., 2011; Evensen et al., 2016). In addition, it seems that the longer an individual is overweight during adolescence and adulthood, the more adverse their level of adipokines and inflammatory markers will be later in life (Murray et al., 2015).

Skinner et al. (2010) showed that multiple inflammatory markers are strongly and positively associated with increasing weight status in children as young as age 3. Although in the present study we did not have inflammatory biomarkers data at those early ages, we observed that being overweight from the age of 2 years onwards was consistently associated with an unfavourable inflammatory score and insulin resistance during adolescence. Other studies have shown that rapid weight gain throughout life (particularly after 2 years of age) was positively related with increased leptin concentrations during childhood (Flexeder et al., 2014), and with increased leptin and CRP levels in young adulthood in males and females (Nazmi et al., 2009). We are not aware of other studies that have measured cardiometabolic outcomes during adolescence using BMI at various time points of age as predictor variable, as we did in the present study.

In a 9–year longitudinal study with children, Gardner et al. (2009) reported that weight alone at 5 years of age presented little relation to BW, but closely predicted weight at 9 years of age. In addition, the authors composed a metabolic score based on insulin resistance, blood pressure, triglycerides, and TC/HDL ratio, and found that it was also poorly predicted by BW, but was associated with weight at 5 years, and even more at 9 years. Our results showed that children who were overweight from the age of 5 presented a higher TC/HDL ratio in adolescence. Another study (Pei et al., 2013) have also reported that the time period at around 5 years of age was a critical period for the development of overweight and obesity, as well as obesity-related factors, supporting the suggestion that a single measure of weight at 5 years of age could provide an indicator to future health for the individual (Gardner et al., 2009).

Our data shows that, during adolescence, BMI maintained a positive association with inflammatory score, HOMA-IR and TC/HDL ratio. Given that the pro-inflammatory state seems to track from adolescence to adulthood (Pirkola et al., 2010), the findings of this report seem to be of interest, because they support and emphasize the potential value of an early screening for unhealthy BMI, and a timely intervention for its improvement during growth, since it may represent an early limiting factor for the acquisition and maintenance of a healthy cardiometabolic profile in later ages (Baker et al., 2007; Juonala et al., 2011).

Our study is not without limitations. First, from the age of 6 years onwards, the routine appointments to the paediatrician become more irregular than in the first years of life, and consequently, anthropometric records were sparse, and due to the loss of data it was impossible to run analyses for later ages. Second, the use of a single measure of each inflammatory biomarker may eventually not reflect a long-term pattern of that specific biomarker. Nevertheless, to somewhat overcome this limitation, we have analyzed several inflammatory biomarkers, which provided us with better global picture of the inflammatory status of the adolescents, and this constitutes one of the strengths of this study. Another strong point of this report is the direct extraction from the written records of data relative to birth and growth until the age of 6 years old, as we did not relied on parent reports.

In conclusion, our results suggest that the maintenance of a high BMI from very early ages was consistently associated with worse inflammatory and lipid profiles, and increased insulin resistance in adolescence. On the other hand, no associations were found between BW and the same analysed outcomes.

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Artigo Original IV

Associations Between Early Life Anthropometric Indicators and Cardiorespiratory Fitness, Physical Activity and Sedentary Time in Adolescence

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ABSTRACT

Introduction: We aimed to explore the associations between early life determinants such as birth weight and BMI at several time points of age (6, 12 and 18 months, and at 2, 3, 4, 5 and 6 years old), with later cardiorespiratory fitness, physical activity and sedentary time in adolescence.

Methods: This is a retrospective school-based study with 539 Portuguese adolescents (292 girls, 247 boys) with a mean age of 13.94±1.62 years. Anthropometric data from birth up to the age of 6 years was extracted from individual child health booklets records, and actual weight and height were measured, and BMI was calculated. Cardiorespiratory fitness was estimated by 20m shuttle run test. Physical activity and sedentary time were assessed with accelerometers. Linear regressions were used to explore the associations between early life anthropometric indicators and cardiorespiratory fitness, physical activity and sedentary time in adolescence.

Results: No associations were found between birth weight and later cardiorespiratory fitness, sedentary time or physical activity in adolescence for both sexes. In girls, BMI at 12 months and at 3 years of age was positively associated with sedentary time in adolescence. From the age of 6 months onwards, in girls, and from the age of 3 years onwards, in boys, BMI was inversely associated with cardiorespiratory fitness in adolescence. No associations were found between BMI at early ages and later physical activity in girls. In boys, we observed positive associations between BMI at the ages of 3, 5 and 6 years old and time spent in some intensities of physical activity in adolescence.

Conclusion: BMI during the early years was consistently negatively associated with later cardiorespiratory fitness in adolescents. The associations between BMI in the yearly years and physical activity and sedentary behaviour in adolescents were scarce and mixed, depending on the sex.

KEYWORDS: Early life anthropometry, cardiorespiratory fitness, physical activity, sedentary time, adolescents.

INTRODUCTION

Overweight and obesity are considered one of the major risk factors for the development of several cardiometabolic abnormalities (Juonala et al., 2011; Twig et al., 2016). The onset of overweight and an eventual evolution to obesity has been occurring increasingly early, and there is strong evidence of the tracking of this condition from early childhood into adolescence and adulthood (Evensen et al., 2016; Freitas et al., 2012).

Due to its important associations with several health parameters, the origins of excessive adiposity have been studied since birth, and even before that (Barker, 2007). Birth weight (BW) is frequently used as a proxy measure of intrauterine development, and both low and high BW have been linked to future obesity (Barker, 2007; Ye et al., 2010); conversely, the potential contribution of BW for impaired future health related-outcomes has also been studied (Chen et al., 2012; Vaag, 2009). However, some authors have been arguing that later obesity and a number of inherent unfavourable events could be more strongly associated with rapid growth during childhood, than with size at birth *per se* (Leunissen et al., 2009). Given that body mass index (BMI) is probably the most simple and widely used anthropometric index to define weight status in large samples (Cole et al., 2000; WHO, 2000), the attention given to its monitoring throughout infancy and childhood could represent a useful indicator for the development of several other characteristics.

Low levels of physical fitness and physical activity, and higher time of sedentary time, have also been associated with a range number of negative health outcomes (Katzmarzyk, 2010; Ortega et al., 2008). Cardiorespiratory fitness (CRF) is a dimension of physical fitness, a recognized powerful marker of health (Ortega et al., 2008), and represents a measure of aerobic functional capacity, reflecting the ability of the body's circulatory and respiratory systems to supply fuel and oxygen during sustained physical activity involving large muscles of the body. Contrary to physical activity and sedentary time, which are considered complex behaviours and therefore its measurement is challenging,

the accurately measure of CRF is considered easier to measure (Ekelund, 2008).

Owing to the importance of these variables, a topic of interest has been whether and how early life anthropometric indicators could be associated with levels of CRF, physical activity and sedentary time in later periods of life. Most of this research has focused their attention on BW and foetal programing (Boreham et al., 2001; Lawlor et al., 2008; Ridgway et al., 2011), and less attention has been paid to the growth period, especially to the development and influence of BMI in the early years (Hallal et al., 2012; Hildebrand et al., 2016; Salonen et al., 2011). In addition, the results of several studies are not unanimous (Andersen et al., 2009; Boreham et al., 2001; Lawlor et al., 2008; Ridgway et al., 2011), precluding consistent conclusions.

Further research examining a more detailed development of several early life anthropometric indicators, assessed in shorter time intervals, and how they associate with later physical activity and fitness levels is therefore needed. Thus, the main objective of this study was to explore the associations between early life determinants such as BW or BMI at several time points of age (6, 12 and 18 months, and at 2, 3, 4, 5 and 6 years old), with CRF, physical activity and sedentary time in adolescence.

MATERIALS, SUBJECTS AND METHODS

Study design and sampling

This study used data from the Longitudinal Analysis of Biomarkers and Environmental Determinants of Physical Activity Study (LabMed Physical Activity Study), a 3-year longitudinal cohort study carried out in five schools in the north of Portugal, with the main objective of assessing the independent and combined associations of dietary intake and fitness levels on blood pressure levels of adolescents. The study protocol and procedures are described in detail elsewhere (Agostinis-Sobrinho et al., 2016; Oliveira-Santos et al., 2016). Briefly, baseline data was collected during the fall of 2011, from an initial sample of 1229 apparently healthy adolescents (12–18 years old) that agreed to

participate in that study. From these, 539 adolescents (292 girls, 247 boys, mean age 13.9 ± 1.6 years) were able to provide the child health booklets records for complete early life data extraction, matching information with cardiorespiratory fitness, physical activity and sedentary time, and compose the final sample for the present study.

This study was conducted in accordance to the Helsinki Declaration for Human Studies of 1975, as revised in 2013 (World Medical Association, 2013), and approved by the Portuguese Data Protection Authority (#1112434/2011) and the Portuguese Ministry of Science and Education (0246200001/2011). All participants were informed of this study aims, and all procedures were carried out with the adequate agreement of the subjects, and written informed consent was obtained from participating adolescents and their parents/tutors.

Early life data collection

Information on pregnancy, prenatal, birth, postnatal and growth periods was retrospectively collected from individual child health booklets records, called *Boletim de Saúde Infantil e Juvenil*, provided by the participants. All weight, length and height measurements available from birth up to the age of 6 years, which were performed and registered on the health booklets by the paediatricians during regular appointments with the participants, were extracted for the present analysis. Subjects were considered born with low BW (<2500g), adequate BW (2500–4000g), or high BW (>4000g) according World health Organization (WHO) recommendations (WHO & UNICEF, 2004). BMI from birth until the age of 2 years was calculated as weight divided by length squared (Kg/m^2), and from 2 years onward calculated as weight divided by squared height (Kg/m^2). From birth and at 6, 12 and 18 months, and at 2, 3, 4, 5 and 6 years of age, all participants were then classified as being normal weight or overweight/obese, according the BMI-for-age percentiles sex specific references, provided by the WHO (2007, 2006).

Anthropometric measurements

Anthropometric measures such as height and weight were collected according standardized procedures (Lohman et al., 1988). BMI was calculated as previously described (Kg/m^2), and all the adolescents were classified in two categories as underweight/normal weight or overweight/obese, using the age and sex-specific BMI-for-age percentiles cut-off values proposed by the World Health Organization (WHO, 2007).

Body fat percentage (BF%) was estimated by bioelectrical impedance (Tanita Inner Scan BC 532, Tokyo, Japan) according to manufacturer's instructions. In order to minimize eventual errors and variations in the BF% assessment, participants were asked to fast overnight, not to drink any fluid four hours prior to their test, urinate within 30 min of test and not to perform any physical exercise in that morning (Dixon et al., 2013; Goss et al., 2003).

Pubertal stage assessment

Pubertal stages of sexual maturation (A - breast development in girls; genital development in boys; and B – pubic hair development, for both sexes) were self-assessed by the participants according to the classification by Tanner (1962), in a private place, and then communicated in a closed envelope to a researcher of the same sex, with stage 1 being pre-pubertal, and 5 being adult maturation. Due to the low number of subjects at Tanner stage 1, they were integrated with Tanner stage 2 and formed the pre-pubertal group.

Cardiorespiratory fitness assessment

CRF was estimated using data from the 20-metre shuttle run test, which has proven to be a feasible, valid and reliable field-test in young people (Ruiz et al., 2011). Participants were required to run straight back and forth between two lines set 20 meters apart. Running speed started at 8.5km/h, increasing levels by 0.5km/h each minute, and reaching 18km/h at minute 20. Each level was announced on a sound device. Participants were instructed to keep pace

according to the audio signals until exhaustion, and encouraged to keep running as long as possible throughout the course of the test. The test was finished when the participant failed to reach the end lines concurrent with the audio signals on two consecutive occasions, or when the subject stopped because of fatigue. The test was performed once, and the total number of shuttles performed by each participant was recorded to posterior calculation of VO_2max, using the equation proposed by Mahar et al. (2011), which in addition to the constants, takes into account in its calculation the number of laps, BMI, gender and age.

Physical activity and sedentary time assessment

Daily physical activity and sedentary time were assessed using accelerometers GT1M (ActiGraph, Pensacola, Florida, USA). Participants were asked to wear the accelerometer attached on the right side of the hip, with the notch faced upwards, during the waking hours of five consecutive days (three weekdays, two weekend days), and to remove it during water-based activities and sleep time. The epoch length was set to 2 seconds to allow a more detailed estimate of physical activity intensity. Accelerometer data were analysed by an automated data reduction program (ActivLive 6.12, ActiGraph, Pensacola, Florida, USA). Participants had to have at least 10 hours of data to count as a valid day to be included, and periods with 60 minutes of consecutive zeros were identified and labelled as non-wear time. After screening, the raw activity "counts" was processed for determination of time spent in the different physical activity intensities. The counts per minute (cpm) cut-points proposed by Evenson et al. (2008) and Trost et al. (2011) were used to determine sedentary time (≤100 cpm) and physical activity intensities [light intensity physical activity (LPA): >100- < 2296 cpm; moderate intensity physical activity (MPA): ≥2296 - <4012 cpm; vigorous intensity physical activity (VPA): ≥4012 cpm; moderate-to-vigorous intensity physical activity (MVPA): ≥2296 cpm].

Socioeconomic Status

The Family Affluence Scale (FAS) (Currie et al., 2008) was used as a proxy measure of adolescent's socioeconomic status. This scale is a four-item questionnaire regarding information on vehicles, home, lifestyle and access to technology, with a range of scores from 0 to 9 points, allowing adolescents to indirectly report their family income. The highest score corresponds to the highest socioeconomic level.

KIDMED index

The KIDMED index (Serra-Majem et al., 2004) (Mediterranean Diet Quality Index for children and adolescents) was used to assess the degree of adherence to the Mediterranean diet, considered a healthy dietary model and associated to a lower occurrence of cardiometabolic diseases (Ros et al., 2014) and certain cancer types (Schwingshackl & Hoffmann, 2015). This index is based on a 16 questions self-administered, which sustain principles of Mediterranean dietary patterns as well as those that undermine it. Questions indicating a negative connotation with respect to the Mediterranean diet were assigned a value of -1 and those with a positive aspect +1. The sum of the values ranges from 0 to 12, where a higher index means good adherence to the Mediterranean diet.

Statistical analyses

Descriptive statistics are presented as means and standard deviations. Two-sided Student’s t-test was used to compare groups for continuous variables and chi-square test for categorical variables.

Linear regression analyses were used to explore the associations between BW and BMI at each time point during the yearly years on CRF, physical activity and sedentary time in adolescence. Regression analyses were adjusted for age, pubertal stage, BMI, BF%, adherence to a Mediterranean dietary pattern (KIDMED index) and socioeconomic status to isolate any

influence of these variables on the results, and the coefficient of determination was used to confirm the variance explained in the model.

Analysis of Covariance with Bonferroni post-hoc multiple comparison tests was used to search for differences in CRF, time spent at certain intensities of daily physical activity, and sedentary time during adolescence, between children born with low weight, normal weight or high weight, and between non overweight and overweight children at each time point until the age of 6 years. Covariates included were age, pubertal stage, BMI, BF%, socioeconomic status and KIDMED index. A p value ≤0.05 was considered statistically significant.

Replication of all the analyses without twins (n=13, 2.4%) and preterm deliveries (n=39, 7.2%), which could hypothetically represent a foetal sub development, did not presented any different result, as in other studies (Peneau et al., 2011). Therefore, for this report we included all the 539 participants who make up this sample.

Data was analysed using the Statistical Package for Social Sciences version 24.0 (SPSS, IBM Corp., NY, USA). A p-value ≤0.05 was considered to denote statistical significance.

RESULTS

Participants' characteristics are shown in Table 1. Boys were taller and heavier than girls, but girls presented greater BF% (p≤0.05). In relation to early life data, boys presented significantly higher values on BW, birth length, and BMI at 6, 12 and 18 months of age (p≤0.05 for all). CRF and daily time of physical activity at all intensities were significantly higher in boys.

Table 1. Characteristics of the Participants at Early Life and Adolescence Periods

	All (*n* = 539)	**Girls (*n* = 292)**	**Boys (*n* = 247)**
Variables	Mean (SD)	Mean (SD)	Mean (SD)
Age (years)	13.94 (1.62)	13.98 (1.63)	13.89 (1.61)
Height (cm)	158.7 (9.00)	156.8 (6.7)	160.9 (10.8) **
Weight (Kg)	53.56 (12.28)	52.16 (10.53)	55.22 (13.92) *
BMI (Kg/m^2)	21.11 (3.73)	21.14 (3.74)	21.09 (3.72)
UW+NW (n; %)	361; 67%	208; 71.2%	153; 61.9%
OW+OB (n; %)	178; 33%	84; 28.8%	94; 38.1%
BF (%)	21.04 (8.00)	25.06 (6.86)	16.29 (6.52) **
Birth Weight (g)	3 772 (482)	3 177 (477)	3 386 (465) **
Birth Length (cm)	49.1 (2.2)	48.6 (2.2)	49.7 (2.0) **
BMI at birth (Kg/m^2)	13.52 (1.39)	13.41 (1.39)	13.66 (1.38) *
BMI at 6 months (Kg/m^2)	17.40 (1.57)	17.09 (1.42)	17.78 (1.65) **
BMI at 12 months (Kg/m^2)	17.72 (1.57)	17.34 (1.41)	18.17 (1.64) **
BMI at 18 months (Kg/m^2)	17.15 (1.43)	16.89 (1.35)	17.45 (1.48) **
BMI at 2 years (Kg/m^2)	18.81 (1.48)	16.70 (1.41)	16.94 (1.55)
BMI at 3 years (Kg/m^2)	16.52 (1.64)	16.39 (1.64)	16.66 (1.63)
BMI at 4 years (Kg/m^2)	16.55 (1.85)	16.45 (1.85)	16.66 (1.86)
BMI at 5 years (Kg/m^2)	16.74 (2.13)	16.67 (2.12)	16.82 (2.15)
BMI at 6 years (Kg/m^2)	17.08 (2.45)	16.89 (2.35)	17.32 (2.56)
Pubertal stage A (%)			
Stage ≤ II	9.3	4.8	14.6
Stage III	34.5	32.9	36.4
Stage IV	43.6	49.0	37.2
Stage V	12.6	13.4	11.7
Pubertal stage B (%)			
Stage ≤ II	8.0	3.8	13.0
Stage III	23.7	24.0	23.5
Stage IV	49.4	47.6	51.4
Stage V	18.9	24.7	12.1
KIDMED index	7.13 (2.02)	7.25 (1.96)	6.98 (2.07)
Socioeconomic status	6.47 (1.62)	6.56 (1.63)	6.36 (1.61)
CRF (ml O_2/Kg/min)	45.69 (7.72)	41.53 (5.23)	50.61 (7.29) **
SED time (min/day)	539.70 (67.06)	536.90 (65.21)	543.20 (69.31)
LPA (min/day)	108.63 (29.49)	100.59 (26.09)	118.67 (30.46) **
MPA (min/day)	32.56 (11.30)	30.28 (11.15)	35.42 (10.86) **
VPA (min/day)	23.25 (11.89)	19.36 (10.20)	28.10 (12.10) **
MVPA (min/day)	55.81 (20.50)	49.64 (18.02)	63.52 (20.84) **
Total PA (min/day)	164.44 (43.27))	150.23 (36.13)	182.19 (44.96) **

$^*p < 0.05$; $^{**}p < 0.001$ for sex comparisons (two-tailed t-tests for continuous variables or chi-square for categorical variables).

Abbreviations: BF%, body fat percentage; BMI, body mass index (WHO, 2006; 2017); UW+NW, underweight + normal weight; OW+OB, overweight + obese; CRF, cardiorespiratory fitness (ml O2/Kg/min); PA, physical activity; LPA, light intensity physical activity; MPA, moderate intensity physical activity; MVPA, moderate-to-vigorous intensity physical activity; VPA, vigorous intensity physical activity; SED time, sedentary time; SD, standard deviation.

The associations of BW and BMI at several time points of age with CRF, sedentary time, and physical activity at different intensities, for each sex, are presented in tables 2 and 3.

Table 2. Linear Regression Coefficients, Significance Values and Coefficients of Determination, Examining the Associations of Birth Weight and BMI at Several Time Points of Age of Adolescent Girls, With Cardiorespiratory Fitness, Sedentary Time, and Daily Time of Physical Activity at Different Intensities, after Adjustment for Age, Pubertal Stage, BMI, BF%, Socioeconomic Status and KIDMED Index at Adolescence

		Dependent Variables					
		CRF	**SED time**	**LPA**	**MPA**	**VPA**	**MVPA**
		ml/Kg/min	**min/day**	**min/day**	**min/day**	**min/day**	**min/day**
Birth weight	B (*p* value)	- 8.709 (0.888)	0.006 (0.532)	- 6.211 (0.999)	- 0.002 (0.165)	- 0.004 (0.104)	- 0.006 (0.112)
	r^2	0.079	0.043	0.052	0.015	0.029	0.029
BMI at 6 months	B (*p* value)	**- 0.889 (< 0.001)**	1.967 (0.569)	- 0.247 (0.856)	0.381 (0.543)	- 0.766 (0.164)	- 0.385 (0.697)
	r^2	**0.121**	0.037	0.028	0.013	0.000	- 0.003
BMI at 12 months	B (*p* value)	**- 0.978 (< 0.001)**	**8.461 (0.033)**	1.833 (0.239)	0.328 (0.618)	- 0.231 (0.704)	0.098 (0.927)
	r^2	**0.162**	**0.050**	0.049	0.001	- 0.013	- 0.012
BMI at 18 months	B (*p* value)	**- 0.962 (< 0.001)**	1.137 (0.750)	0.713 (0.605)	- 0.200 (0.729)	- 1.006 (0.062)	- 1.206 (0.185)
	r^2	**0.132**	0.024	0.050	- 0.003	0.009	0.000
BMI at 2 years	B (*p* value)	**- 1.144 (< 0.001)**	0.938 (0.800)	- 0.526 (0.716)	0.047 (0.938)	- 0.288 (0.600)	- 0.242 (0.803)
	r^2	**0.163**	0.024	0.043	0.008	- 0.011	- 0.005
BMI at 3 years	B (*p* value)	**- 1.444 (< 0.001)**	**4.071 (0.019)**	0.241 (0.844)	0.041 (0.935)	- 0.201 (0.660)	- 0.160 (0.841)
	r^2	**0.282**	**0.053**	0.037	0.023	- 0.006	0.014
BMI at 4 years	B (*p* value)	**- 1.505 (< 0.001)**	1.906 (0.517)	- 1.285 (0.301)	- 0.506 (0.297)	- 0.682 (0.140)	- 1.189 (0.129)
	r^2	**0.326**	0.077	0.038	0.052	0.002	0.030
BMI at 5 years	B (*p* value)	**- 1.472 (< 0.001)**	4.027 (0.091)	0.639 (0.544)	0.075 (0.860)	0.169 (0.681)	0.244 (0.734)
	r^2	**0.444**	0.097	0.029	0.039	- 0.012	0.011
BMI at 6 years	B (*p* value)	**- 1.150 (< 0.001)**	2.053 (0.383)	0.985 (0.305)	0.484 (0.212)	0.619 (0.097)	1.102 (0.077)
	r^2	**0.366**	0.018	0.049	0.027	0.006	0.023
Current BMI	B (*p* value)	**- 1.100 (< 0.001)**	1.997 (0.084)	**1.489 (0.001)**	**0.439 (0.028)**	0.148 (0.424)	0.587 (0.071)
	r^2	**0.678**	0.054	**0.097**	**0.028**	- 0.006	0.012

Abbreviations: BMI, body mass index; B, linear regression coefficient; CRF, cardiorespiratory fitness (ml O_2/Kg/min); LPA, light intensity physical activity; MPA, moderate intensity physical activity; MVPA, moderate-to-vigorous intensity physical activity; *p*, significance value; r^2, coefficient of determination; SED time, sedentary time; VPA, vigorous intensity physical activity.

Table 3. Linear Regression Coefficients, Significance Values and Coefficients of Determination, Examining the Associations of Birth Weight and BMI at Several Time Points of Age of Adolescent Boys, With Cardiorespiratory Fitness, Sedentary Time, and Daily Time of Physical Activity at Different Intensities, after Adjustment for Age, Pubertal Stage, BMI, BF%, Socioeconomic Status and KIDMED Index at Adolescence

		Dependent Variables					
		CRF	**SED time**	**LPA**	**MPA**	**VPA**	**MVPA**
		ml/Kg/min	**min/day**	**min/day**	**min/day**	**min/day**	**min/day**
Birth weight	B (*p* value)	0.002 (0.888)	0.009 (0.451)	0.003 (0.502)	0.002 (0.294)	0.003 (0.079)	0.005 (0.116)
	r^2	0.122	- 0.001	0.249	0.034	0.051	0.054
BMI at 6 months	B (*p* value)	- 0.032 (0.912)	0.481 (0.893)	- 0.641 (0.649)	0.431 (0.434)	0.414 (0.499)	0.844 (0.421)
	r^2	0.111	- 0.008	0.235	0.044	0.028	0.046
BMI at 12 months	B (*p* value)	- 0.422 (0.190)	2.961 (0.454)	0.579 (0.711)	0.816 (0.185)	0.664 (0.338)	1.480 (0.210)
	r^2	0.146	- 0.011	0.232	0.048	0.010	0.036
BMI at 18 months	B (*p* value)	- 0.458 (0.158)	2.829 (0.456)	0.735 (0.619)	0.688 (0.246)	0.598 (0.360)	1.286 (0.254)
	r^2	0.110	- 0.004	0.221	0.029	0.009	0.025
BMI at 2 years	B (*p* value)	- 0.494 (0.136)	1.053 (0.779)	0.458 (0.745)	0.591 (0.319)	0.919 (0.147)	1.510 (0.174)
	r^2	0.092	- 0.013	0.228	0.026	0.021	0.031
BMI at 3 years	B (*p* value)	**- 1.124 (< 0.001)**	- 1.200 (0.742)	**2.231 (0.019)**	**0.136 (0.017)**	1.404 (0.223)	**2.763 (0.010)**
	r^2	**0.154**	- 0.007	**0.252**	**0.058**	0.045	**0.066**
BMI at 4 years	B (*p* value)	**- 1.034 (< 0.001)**	0.006 (0.999)	1.278 (0.321)	0.709 (0.192)	0.156 (0.790)	0.865 (0.394)
	r^2	**0.193**	- 0.013	0.249	0.031	0.013	0.028
BMI at 5 years	B (*p* value)	**- 1.454 (< 0.001)**	2.497 (0.461)	**3.131 (0.021)**	**1.027 (0.044)**	1.558 (0.207)	**2.585 (0.009)**
	r^2	**0.280**	- 0.007	**0.267**	**0.095**	0.096	**0.116**
BMI at 6 years	B (*p* value)	**- 1.423 (< 0.001)**	- 1.311 (0.621)	**1.728 (0.039)**	**1.218 (0.003)**	0.706 (0.141)	**1.924 (0.017)**
	r^2	**0.370**	0.019	**0.256**	**0.110**	0.030	**0.079**
Current BMI	B (*p* value)	**- 1.406 (< 0.001)**	- 0.353 (0.810)	1.145 (0.093)	0.267 (0.238)	- 0.133 (0.596)	0.133 (0.758)
	r^2	**0.598**	- 0.004	0.265	0.036	0.036	0.041

Abbreviations: BMI, body mass index; B, linear regression coefficient; CRF, cardiorespiratory fitness (ml O_2/Kg/min); LPA, light intensity physical activity; MPA, moderate intensity physical activity; MVPA, moderate-to-vigorous intensity physical activity; *p*, significance value; r^2, coefficient of determination; SED time, sedentary time; VPA, vigorous intensity physical activity.

From the age of 6 months in girls, and from 3 years in boys, it was observed a consistent inverse association between BMI at several ages and CRF in adolescence.

In girls, BMI at 12 months and at 3 years of age was positively associated with sedentary time in adolescence, and BMI at adolescence was positively associated with LPA and MPA. In boys, BMI at 3, 5 and 6 years was positively associated with LPA, MPA and MVPA.

Tables 4 and 5 display the analysis of covariance of CRF, sedentary time

and physical activity at different intensities of adolescent´s girls and boys, accordingly BW category and BMI status at several time points of age.

Table 4. Analyses of Covariance of Values of Cardiorespiratory Fitness, Sedentary Time and Daily Time of Physical Activity at Different Intensities of Adolescent Girls, Accordingly Their Birth Weight Category and BMI Status at Several Time Points of Age, Adjusted for Age, Pubertal Stage, BMI, Body Fat Percentage, Socioeconomic Status and KIDMED Index

		CRF ml/Kg/min	SED time min/day	LPA min/day	MPA min/day	VPA min/day	MVPA min/day
		Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)
Birth weight	LOW	42.95 (1.03)	535.29 (15.98)	94.99 (6.37)	32.05 (2.78)	20.45 (2.51)	57.51 (4.45)
	NORMAL	41.43 (0.31)	536.09 (4.48)	101.27 (1.79)	30.25 (0.78)	18.95 (0.70)	49.19 (1.25)
	HIGH	40.79 (1.57)	560.74 (22.63)	94.78 (9.02)	27.50 (3.93)	17.59 (3.55)	45.09 (6.30)
BMI at 6 months	UW+NW	42.18 (0.34)**	533.22 (5.02)	99.96 (2.01)	30.74 (0.91)	19.28 (0.79)	50.02 (1.43)
	OW+OB	39.45 (0.84)	551.33 (13.06)	95.73 (5.22)	27.53 (2.37)	15.78 (2.08)	43.31 (3.72)
BMI at 12 months	UW+NW	42.29 (0.45)*	529.37 (6.84)*	99.46 (2.72)	30.09 (1.15)	19.44 (1.04)	49.53 (1.85)
	OW+OB	40.90 (0.66)	553.92 (10.03)	99.19 (3.99)	29.99 (1.68)	18.23 (1.53)	48.22 (2.72)
BMI at 18 months	UW+NW	42.06 (0.39)*	535.54 (6.01)	99.68 (2.32)	30.59 (0.98)	20.19 (0.89)	50.79 (1.52)
	OW+OB	40.59 (0.50)	537.59 (7.77)	99.06 (3.00)	29.63 (1.26)	17.89 (1.16)	47.51 (1.97)
BMI at 2 years	UW+NW	42.77 (0.43)***	535.99 (6.88)	100.32 (2.69)	30.11 (1.12)	19.39 (1.01)	49.50 (1.79)
	OW+OB	40.41 (0.48)	541.91 (7.87)	100.13 (3.08)	29.70 (1.28)	18.18 (1.16)	47.88 (2.05)
BMI at 3 years	UW+NW	42. 84(0.37)***	526.40 (6.31)**	100.03 (2.52)	29.99 (1.05)	19.51 (0.96)	49.49 (1.64)
	OW+OB	38.64 (0.50)	554.06 (8.19)	104.52 (3.28)	30.13 (1.36)	18.95 (1.24)	49.08 (2.12)
BMI at 4 years	UW+NW	42.95 (0.43)***	527.14 (6.60)	101.47 (2.81)	30.67 (1.10)	20.19 (1.04)	50.86 (1.76)
	OW+OB	38.81 (0.58)	549.19 (8.60)	103.17 (3.66)	28.97 (1.43)	17.98 (1.35)	46.95 (2.29)
BMI at 5 years	UW+NW	43.23 (0.39)***	530.06 (6.75)	100.50 (2.99)	29.91 (1.22)	18.40 (1.17)	48.31 (2.04)
	OW+OB	37.79 (0.51)	542.72 (8.33)	100.48 (3.67)	29.42 (1.51)	20.29 (1.44)	49.71 (2.52)
BMI at 6 years	UW+NW	43.55 (0.40)***	530.44 (7.49)	97.93 (3.07)	29.59 (1.26)	17.41 (1.17)	47.01 (1.99)
	OW+OB	38.79 (0.46)	543.99 (8.32)	104.12 (3.40)	30.56 (1.39)	21.72 (1.30)	52.28 (2.21)
Current BMI	UW+NW	43.29 (0.21)***	533.01 (4.35)	99.21 (1.79)	30.17 (0.72)	19.72 (0.86)	49.89 (1.30)
	OW+OB	36.26 (0.32)	540.67 (6.87)	107.99 (2.84)	32.99 (1.14)	20.73 (1.36)	53.65 (2.05)

*$p \leq 0.05$; **$p < 0.01$; ***$p < 0.001$

Abbreviations: BMI, body mass index (WHO, 2006; 2017); CRF, cardiorespiratory fitness; UW+NW, underweight + normal weight; OW+OB, overweight + obese; LPA, light intensity physical activity; MPA, moderate intensity physical activity; MVPA, moderate-to-vigorous intensity physical activity; VPA, vigorous intensity physical activity; SED time, sedentary time.

Table 5. Analyses of Covariance of Values of Cardiorespiratory Fitness, Sedentary Time and Daily Time of Physical Activity at Different Intensities of Adolescent Boys, Accordingly Their Birth Weight Category and BMI Status at Several Time Points of Age, Adjusted for Age, Pubertal Stage, BMI, Body Fat Percentage, Socioeconomic Status and KIDMED Index

		CRF ml/Kg/min	SED time min/day	LPA min/day	MPA min/day	VPA min/day	MVPA min/day
		Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)
Birth weight	LOW	49.84 (2.26)	571.28 (15.98)	131.34 (10.81)	35.31 (4.39)	28.34 (4.86)	63. 65 (8.33)
	NORMAL	50.33 (0.46)	541.02 (5.46)	117.52 (2.06)	35.01 (0.84)	27.60 (0.93)	62.62 (1.59)
	HIGH	54.45 (1.61)	558.81 (20.22)	128.02 (7.62)	40.91 (3.09)	34.79 (3.42)	75.70 (5.87)
BMI at 6 months	UW+NW	50.31 (0.54)	542.03 (6.71)	120.53 (2.62)	35.16 (1.04)	27.75 (1.15)	62.91 (1.98)
	OW+OB	49.94 (0.96)	545.54 (11.38)	113.97 (4.45)	34.51 (1.76)	28.29 (1.95)	62.81 (3.53)
BMI at 12 months	UW+NW	50.59 (0.69)*	544.78 (8.91)	119.21 (3.847)	33.88 (1.38)	26.59 (1.55)	60.47 (2.64)
	OW+OB	48.19 (0.75)	553.24 (9.65)	124.27 (3.76)	35.78 (1.49)	29.36 (1.68)	65.15 (2.86)
BMI at 18 months	UW+NW	50.86 (0.64)	544.68 (7.63)	118.63 (2.96)	35.26 (1.19)	27.91 (1.32)	63.17 (2.28)
	OW+OB	49.63 (0.72)	550.32 (8.87)	120.76 (3.44)	35.85 (1.39)	28.32 (1.53)	64.17 (2.65)
BMI at 2 years	UW+NW	51.89 (0.65)**	548.58 (7.69)	119.51 (2.89)	35.18 (1.22)	27.36 (1.29)	62.54 (2.28)
	OW+OB	48.94 (0.78)	540.68 (9.56)	121.04 (3.58)	36.07 (1.52)	30.09 (1.61)	66.16 (2.83)
BMI at 3 years	UW+NW	51.74 (0.61)**	548.08 (7.72)	115.45 (2.98)*	33.69 (1.21) *	26.73 (1.31)	60.42 (2.27) *
	OW+OB	49.08 (0.81)	549.23 (9.67)	125.56 (3.74)	38.24 (1.51)	30.24 (1.65)	68.47 (2.84)
BMI at 4 years	UW+NW	51.24 (0.66)*	548.61 (8.87)	118.71 (3.17)	34.42 (1.33)	27.44 (1.44)	61.86 (2.49)
	OW+OB	48.95 (0.82)	541.08 (10.62)	121.49 (3.79)	37.35 (1.59)	29.56 (1.72)	66.91 (2.97)
BMI at 5 years	UW+NW	52.48 (0.69)***	540.44 (9.11)	114.56 (3.61)*	32.96 (1.37) *	26.23 (1.59)	59.19 (2.69) *
	OW+OB	47.79 (0.74)	555.61 (9.53)	127.77 (3.77)	37.89 (1.44)	30.98 (1.67)	68.88 (2.81)
BMI at 6 years	UW+NW	53.04 (0.76)***	548.99 (10.43)	117.97 (4.01) *	32.82 (1.60) *	27.19 (1.89)	60.02 (3.15) *
	OW+OB	47.27 (0.71)	546.50 (9.07)	124.35 (3.49)	38.39 (1.39)	30.09 (1.64)	68.49 (2.74)
Current BMI	UW+NW	55.05 (0.27)***	543.18 (4.99)	114.21 (1.85)	34.70 (0.81)	27.75 (0.90)	62.45 (1.49)
	OW+OB	45.61 (0.41)	544.60 (7.04)	118.43 (2.60)	36.90 (1.14)	27.40 (1.27)	64.30 (2.10)

*$p \leq 0.05$; **$p < 0.01$; ***$p < 0.001$

Abbreviations: BMI, body mass index (WHO, 2006; 2017); CRF, cardiorespiratory fitness; UW+NW, underweight + normal weight; OW+OB, overweight + obese; LPA, light intensity physical activity; MPA, moderate intensity physical activity; MVPA, moderate-to-vigorous intensity physical activity; VPA, vigorous intensity physical activity; SED time, sedentary time.

No differences were observed for CRF, sedentary time or physical activity in adolescence, regardless having born with low, normal or high weight, for both sexes.

From the age of 6 months onwards, girls who were normal weight during childhood presented higher CRF in adolescence than girls who were overweight. In boys, with the exception of BMI at the age of 18 months, from the age of 12 months ahead, those who were normal weight during their childhood

also presented a higher CRF in adolescence.

Regarding physical activity, girls who were overweight at the ages of 12 months and 3 years, presented significantly higher amount of sedentary time in adolescence when compared with normal weight girls at those ages. In boys, those who were overweight at the ages of 3, 5 and 6 years presented more time of LPA, MPA and MVPA in adolescence.

DISCUSSION

This study showed consistent associations between those subjects assigned to a normal weight category during their childhood, and a better CRF later in adolescence. However, those associations were not seen for sedentary time nor for some physical activity intensities. Likewise, BW didn't show statistically significant associations with CRF, sedentary time and physical activity, regardless of sex.

Birth weight, cardiorespiratory fitness, physical activity and sedentary time

Our results are in agreement with other studies which have reported that BW does not seem to be associated with CRF (Ortega et al., 2009; Salonen et al., 2011), and have limited influence on later sedentary time (Hallal et al., 2006) or physical activity (Mattocks et al., 2008) in late childhood and adolescence periods, suggesting that the foetal programming of this parameters is unlikely (Hallal et al., 2006).

In the present study sample, only 5.9% of the subjects have born with low BW (<2500g) and 5.2% with high BW (>4000g), according WHO reference values (WHO & UNICEF, 2004). However, in the adolescence period the combined percentage of overweight and obese individuals in the same sample was about 33%. Given that BW is not modifiable, whereas BMI is, focus on BMI development during childhood should assume greater importance, given that overweight and obesity seem to track throughout life (de Kroon et al., 2011; Evensen et al., 2016), and the reversing of an early unfavourable BMI is

important for preventing several health-risk outcomes, in adulthood (Juonala et al., 2011).

BMI at early years and cardiorespiratory fitness

Our findings of consistent inverse associations between BMI at early years and CRF in adolescence are in line with some studies (Salonen et al., 2011; van Deutekom et al., 2015). van Deutekom et al. (2015) described a negative association between accelerated infant growth from 0–12 months and CRF of children at 8–9 years of age. Conversely, Salonen et al. (2011) found that higher BMI at 11 years predicted lower CRF in adults. Nevertheless, it should be noted that none of these studies targeted adolescents, and to the best of our knowledge, this is the first study with this age range. Trying to fill this gap, we performed a detailed analysis of BMI values from birth until 6 years of age, with 6-months intervals until the age of 2 years, and annually from 2 to 6 years of age. This procedure allowed us to observe that a persistent early unfavourable BMI during growth period seems to be consistently associated with a lower CRF later in adolescence. In addition, as children grew, there were consistent results for an increase in the coefficients of regression and determination, i.e., a better explanation of the associations between early BMI and CRF during adolescence.

BMI at early years, physical activity and sedentary time

Contrary to the consistent findings suggesting an inverse association between BMI and CRF, our results showed a scarcity of associations between early BMI and future physical activity levels or sedentary time. Only in girls a positive association was found between BMI at the ages of 12 months and 3 years, and sedentary time during adolescence. Complementary analysis of covariance showed that girls who were overweight at the age of 12 months, and also at the age of 3 years old, presented significantly more sedentary time in adolescence. In a recent systematic review (Hildebrand et al., 2016), only 2 studies (Fuller-Tyszkiewicz et al., 2012; Hands et al., 2011) were found examining the association between an early BMI and later sedentary time, and the reported associations were also positive. Nonetheless, it must be taken in

account that both assessments of sedentary time in those studies were based on parent-reported TV-time, and not through accelerometry, as in the present study.

Some studies (Hallal et al., 2006, 2012) support that weight gain during infancy and childhood does not seem to be a major determinant of physical activity levels during adolescence. At least for girls, our results are in agreement with this, as we did not found any associations between early BMI and later physical activity levels. In boys, we have found mixed results. At the ages of 3, 5 and 6 years old, we observed positive associations between BMI and several intensities of physical activity, and analysis of covariance confirmed higher time of LPA, MPA and MVPA in adolescents who were overweight at those ages. Interestingly, these results are the opposite to what we expected, and further research using the same approach of this study would be of great interest to confirm or confront our findings. Contrary to CRF, which is considered to be a fairly stable state or condition over time (Ekelund, 2008), and where genetics is thought to account for about 40 to 50% of it (Bouchard et al., 1986, 1998), physical activity is a highly variable behaviour that can easily be modified, and as such, is influenced by a complex mixture of biological, social, cultural and environmental factors (Hallal et al., 2012). Additionally, there are some challenges associated to the objectively assessment of physical activity and sedentary time (Ekelund, 2008).

Nonetheless, the objectively assessment of physical activity with accelerometers constitute one of the strengths of this study, as these devices may capture the entire daily pattern of physical activity, and not relying on self-reports; also the direct extraction from written records of early life data relative to birth and growth until the age of 6 years old, and not parentally reported, is also one of the strengths of the present report. However, there are also some limitations that need to be acknowledged. The large loss of early life data after the 6 years of age made it impossible to run analyses for later ages, since the routine appointments to the paediatrician become more irregular than in the first years of life, and anthropometric records became sparse; it would be of great interest in the future to keep a longer follow-up time assessment, but constraints

related with this kind of interventions are well known.

In conclusion, our results show that, from since the early years, a high BMI was consistently negatively associated with CRF during adolescence, in both sexes. Boys presented mixed results regarding physical activity levels. No associations were found between BW and CRF, sedentary time or physical activity during adolescence, regardless genders. For both sexes, there was a consistency of results for adolescents to present a higher CRF if they have been normal weight during their infancy and childhood.

From a public health perspective, the findings from this study are of importance, because they emphasize the potential value of an early screening of an unfavourable BMI status and timely intervention for its improvement during growth, as it may represent an early limiting factor for the acquisition and maintenance of a good CRF later in adolescence.

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CAPÍTULO V

DISCUSSÃO GERAL E CONCLUSÕES

Discussão Geral

Os nossos resultados (Artigo I) indicaram que o peso ao nascer não apresentou capacidade para discriminar entre uma categoria de excesso de peso/obesidade/adiposidade excessiva na adolescência, independentemente da medida de adiposidade utilizada para avaliar essa condição, para ambos os sexos. Gardner et al. (2009) também consideraram o peso ao nascer um preditor pobre, relatando num estudo longitudinal de 9 anos que o peso corporal aos 5 anos de idade apresentava pouca relação com o peso ao nascer; mas em contrapartida previa com exatidão o peso corporal aos 9 anos. No entanto, é de considerar que nesse estudo a única variável a ser predita foi apenas o peso corporal. Outros estudos também não encontraram associações entre o peso ao nascer e algumas medidas de adiposidade avaliadas durante a infância (Wells et al., 2005) e a adolescência (Botton et al., 2008; Labayen et al., 2006), ou então apresentaram resultados mistos (Dubois & Girard, 2006; Rooney et al., 2011).

A primeira geração de estudos acerca da origem de doenças baseada no desenvolvimento fetal em seres humanos relacionou o peso ao nascer com a morbilidade e mortalidade na adultícia, com base na teoria da origem fetal das doenças do adulto proposta por Barker (Barker et al., 2002; Barker et al., 1993a; Barker et al., 1993b; Barker et al., 1989). Nesta teoria o baixo peso ao nascer é usado como *proxy* para um crescimento e nutrição fetal subóptimos e tem sido teoricamente apresentado como um contribuidor para o aumento do risco de doenças crónicas, tais como doença cardíaca e menor tolerância à glicose. Porém, as premissas e conclusões apresentadas nos estudos de Barker e colaboradores baseiam-se em amostras constituídas por sujeitos nascidos nos anos 20 e 30 do século passado, que vários anos depois, já adultos, foram reavaliados relativamente a parâmetros relacionados com a saúde, representando assim uma população que transitou por épocas de escassez e abundância, e que não é o caso atualmente. As transformações socioeconómicas que aconteceram desde essa época em países desenvolvidos são tão profundas, que tornaram as circunstâncias atuais

completamente diferentes daquelas que levaram a uma desnutrição no período intrauterino e, eventualmente, foram causadoras de um baixo peso ao nascer. De facto, é mais provável que estejamos expostos atualmente ao oposto, ou seja, o excesso de peso e obesidade a ser cada vez mais comum entre as mulheres grávidas, que, por consequência, dão à luz bebés com peso ao nascer mais elevado (Blackwell et al., 2016; Ehrenberg et al., 2004; Salonen et al., 2011; Sewell et al., 2006).

Gillman et al. (2013) referem que o peso ao nascer e os seus componentes, a duração gestacional e o desenvolvimento fetal, são reconhecidos atualmente como indicadores momentâneos de baixa precisão, devido a inúmeras influências pré-natais e perinatais, e alguns autores (Gardner et al., 2009; Hallal et al., 2006; Jeffery et al., 2006; Salonen et al., 2011) têm vindo a relativizar a importância dada ao peso ao nascer no desenvolvimento de resultados de saúde posteriores.

Tendo em conta a categoria do peso ao nascer (baixo peso, peso normal, peso elevado) de cada indivíduo, não encontramos quaisquer diferenças nos parâmetros cardiometabólicos avaliados na adolescência (Artigo III), o que vai de encontro aos resultados de outros estudos que sugerem que o peso ao nascer tem vindo a perder relevância nas associações com o risco cardiometabólico em períodos posteriores da vida (Gardner et al., 2009; Jeffery et al., 2006; Rondó et al., 2013). Por exemplo, alguns estudos com crianças e adolescentes reportaram uma ausência de associações entre o peso ao nascer e vários biomarcadores inflamatórios (Cook et al., 2000; Cook et al., 1999; Gillum, 2003; Kim et al., 2006; Rondó et al., 2013). Para além dos dados relativos aos biomarcadores inflamatórios, os nossos resultados estão em linha com os de outros estudos que também não encontraram associações entre o peso ao nascer e outros parâmetros cardiometabólicos, como por exemplo resistência à insulina e perfil lipídico na infância (Bekkers et al., 2011; Jeffery et al., 2006) e adolescência (Horta et al., 2009; Kim et al., 2006). De facto, a ausência ou fraqueza das associações entre um crescimento fetal inadequado, traduzido pelo peso ao nascer, e os perfis lipídicos de adolescentes (Huxley et al., 2004; Owen et al., 2003) e adultos (Libby et al.,

2008; Skidmore et al., 2004), parece ser consistente na literatura.

No entanto, a literatura também tem apresentado resultados mistos, dependendo dos parâmetros cardiometabólicos analisados, mesmo dentro da mesma amostra em estudo. Zhang et al. (2014) reportou que o peso ao nascer mostrou estar inversamente relacionado com os níveis de insulina e HOMA-IR, mas não demonstrou qualquer associação com os níveis de PCR nem do perfil lipídico de crianças e adolescentes dos 6 aos 15 anos de idade.

Da mesma forma que para os parâmetros apresentados anteriormente, não observamos associações entre o peso ao nascer e a aptidão cardiorrespiratória, atividade física e tempo sedentário durante a adolescência, independentemente do sexo (Artigo IV). Os nossos resultados parecem ir de encontro aos de outros estudos que indicaram ausência de associações entre o peso ao nascer e aptidão cardiorrespiratória (Ortega et al., 2009; Salonen et al., 2011) e que sugerem que o peso ao nascer tem uma influência limitada no tempo passado em comportamentos sedentários (Hallal et al., 2006) ou em atividade física (Mattocks et al., 2008; Oglund et al., 2015) durante a infância e a adolescência.

Neste contexto, os nossos resultados relativos às relações entre o peso ao nascer e os parâmetros relacionados com a saúde durante a adolescência não parecem apontar para que a programação fetal seja um fator determinante na inevitabilidade de um evento de saúde negativo na adolescência, tal como sugerido por outros autores (Hallal et al., 2006).

Resultados distintos daqueles observados para o peso ao nascer foram obtidos, em geral, para o desenvolvimento do IMC durante a infância e adolescência. Os nossos dados indicam que o IMC durante a infância, a partir de certa idade e dependendo do sexo, possui capacidade discriminatória para classificar corretamente os indivíduos com adiposidade excessiva durante a adolescência, seja qual for a medida de adiposidade utilizada para avaliar essa condição (Artigo I). Nas raparigas, foi possível verificar que dos 6 meses aos 6 anos de idade, o IMC apresentou capacidade discriminatória para todas as

medidas de adiposidade, com exceção para o rácio cintura/estatura, que apenas se iniciou aos 12 meses. Nos rapazes, observou-se que o poder discriminatório do IMC durante a infância se iniciou mais tarde, nomeadamente aos 12 meses de idade para o IMC, aos 18 meses para o perímetro de cintura e aos 3 anos para a percentagem de massa gorda e para o rácio cintura/estatura. Estes resultados mostraram que a capacidade discriminatória do IMC para todas as medidas de adiposidade, durante a adolescência, foi significativa em idades mais precoces nas raparigas do que nos rapazes, o que pode sugerir que uma condição de excesso de peso ou obesidade que se inicie na infância pode prolongar-se durante mais tempo nas raparigas, uma vez que parece iniciar-se mais cedo.

Nos nossos resultados foi igualmente possível verificar que a capacidade discriminatória do IMC aumentou à medida que as crianças cresciam, sendo que os 5 anos de idade, para as raparigas, e os 6 anos, para os rapazes, foram as idades com o melhor poder discriminatório para identificar corretamente uma categoria desfavorável de adiposidade na adolescência, para todas as medidas, com áreas sob a curva sempre acima de 0,8.

Estes dados reforçam a utilidade e importância da monitorização do IMC desde idades muito precoces, uma vez que demonstra ser um método simples, mas eficaz, na identificação e prevenção de uma condição de excesso de peso à posteriori, não só para o IMC, mas também para outras medidas de adiposidade, como percentagem de massa gorda estimada por bioimpedância, perímetro de cintura ou rácio cintura/estatura, tanto em raparigas como em rapazes.

Alguns estudos têm demonstrado que medidas de adiposidade geral (Ford et al., 2001; Visser et al., 2001) e abdominal (Brooks et al., 2010; Vikram et al., 2003) se associam a uma série de biomarcadores inflamatórios e metabólicos. Da mesma forma, dados relativos ao *National Health and Nutrition Examination Survey* (Ford, 2003; Ford et al., 2005; Ford et al., 2001) sugerem que o IMC é um bom preditor de níveis aumentados de PCR em crianças. Dado o exposto, colocámos a hipótese de as medidas de adiposidade, para

além de terem capacidade em identificar uma condição de excesso de peso/obesidade, poderem também ser úteis como indicadores indiretos dos níveis de biomarcadores inflamatórios e metabólicos, em adolescentes (Artigo II). Os resultados sugeriram que, ao nível de grupo, é possível definir pontos de corte para cada medida de adiposidade, acima dos quais é provável encontrar valores mais elevados de certos biomarcadores. Além disso, concluímos que as pequenas diferenças no poder discriminatório entre as medidas de adiposidade não são significativas e, como tal, serão de relevância limitada, não permitindo para este efeito a adoção de uma única medida de obesidade preferencialmente a todas as outras. Por sua vez, esta conclusão veio sugerir que o IMC não é inferior a outros métodos ou técnicas para esse propósito.

O ponto apresentado anteriormente é importante devido ao facto dos nossos resultados, no Artigo III, terem mostrado que uma condição de excesso de peso ou obesidade a partir dos 2 anos de idade, identificada pelo IMC, estava consistentemente associada a um perfil inflamatório desfavorável e a maior resistência à insulina, durante a adolescência. Outros estudos mostraram que o aumento rápido de peso (particularmente após os 2 anos de idade) foi positivamente relacionado com o aumento das concentrações de leptina durante a infância (Flexeder et al., 2014), e com níveis aumentados de leptina e PCR em jovens adultos de ambos os sexos (Nazmi et al., 2009). Também Singhal et al. (2003) referem que parece ser a aceleração precoce do crescimento que exerce efeitos adversos na programação da resistência à insulina, independentemente do peso ao nascer. Os nossos resultados vão de encontro a estas perspectivas, reforçando a necessidade duma maior relevância e atenção atribuídas ao crescimento no período pós-natal, uma vez que esta fase poderá ser mais favorável à intervenção em relação aos fatores de risco para doenças cardiovasculares em idades futuras (Singhal & Lucas, 2004).

Apesar da avaliação de biomarcadores inflamatórios não ser um procedimento habitual em crianças, Skinner et al. (2010) verificaram que, mesmo em idades muito precoces, o processo inflamatório parece seguir o mesmo padrão daquele que se verifica em idades mais avançadas. Estes

autores (Skinner et al., 2010) encontraram associações robustas entre vários biomarcadores inflamatórios e um estatuto de obesidade em crianças com idades tão novas quanto 3 anos. Embora no Artigo III não tenhamos recolhido dados relativos a biomarcadores em idades tão jovens quanto o estudo referido anteriormente, e como tal não temos informação acerca da hipótese de em idades mais precoces já se verificar uma associação entre adiposidade e inflamação (que observamos na adolescência), é possível que essa relação já exista desde cedo, como Skinner et al. (2010) reportaram, e que permaneça até à adolescência.

Os nossos resultados mostraram associações significativas entre o IMC durante os primeiros anos de vida e o rácio CT/HDL na adolescência, a partir de idades mais tardias do que para a inflamação de baixo grau e para a resistência à insulina. Apenas aos 5 e 6 anos foi possível verificar que crianças que tinham excesso de peso também apresentaram, em média, um rácio CT/HDL significativamente mais elevado na adolescência, do que as crianças que à mesma idade apresentavam um estatuto normoponderal. O período de tempo a rondar os 5 anos de idade foi também apontado por outros autores (Gardner et al., 2009; Pei et al., 2013) como um período crítico, não apenas para o desenvolvimento de excesso de peso ou obesidade, mas também de outros parâmetros relacionados com estas condições. Gardner et al. (2009) apresentaram um score metabólico, composto por variáveis recolhidas aos 9 anos de idade relativas à resistência à insulina, tensão arterial, triglicerídeos e rácio CT/HDL, e reportaram que este score era fracamente predito pelo peso ao nascer, mas que estava associado com o peso corporal aos 5 anos.

De acordo com os resultados do Artigo IV, o IMC nos primeiros anos de vida e a aptidão cardiorrespiratória na adolescência associaram-se inversamente e de forma consistente; associações essas que se foram tornando mais fortes e com melhor poder explicativo à medida que as crianças cresciam. Embora visando idades diferentes aquando da medição do IMC e aptidão cardiorrespiratória, outros estudos (Salonen et al., 2011; van Deutekom et al., 2015) reportaram associações no mesmo sentido que as encontradas no

nosso. Apesar de os nossos resultados terem mostrado, para os participantes de ambos os sexos, e de forma consistente, que aqueles que durante a infância tiveram uma condição normoponderal apresentaram, em média, uma aptidão cardiorrespiratória significativamente mais elevada na adolescência, nas raparigas essa associação mostrou-se evidente mais cedo, logo a partir dos 6 meses de idade, enquanto que nos rapazes as associações apenas se mostraram significativas a partir dos 3 anos de idade. Esta associação manteve-se no período da adolescência, ou seja, os indivíduos normoponderais apresentaram valores de aptidão cardiorrespiratória mais elevados. Este ponto parece-nos relevante, uma vez que a aptidão cardiorrespiratória constitui-se como um poderoso indicador de saúde (Ortega et al., 2008b) e um IMC desfavorável desde idades muito jovens pode constituir um fator limitante para um desenvolvimento favorável desta dimensão da aptidão física.

Em contraste com os resultados observados entre o IMC durante a infância e a aptidão cardiorrespiratória, não foram observadas associações similarmente consistentes para o tempo sedentário e a atividade física, na adolescência (Artigo IV). Para as raparigas, os nossos resultados não indicaram quaisquer associações entre valores de IMC desde o nascimento até aos 6 anos de idade e níveis de atividade física na adolescência, estando em linha com os resultados provenientes do *Pelotas Birth Cohort Study* (Hallal et al., 2012; Hallal et al., 2006). Nesse estudo os autores sugerem que o ganho de peso durante a infância não parece ser um determinante fundamental que explique os níveis de atividade física durante a adolescência. Nos rapazes, encontramos resultados mistos, com ausência de associações entre IMC até aos 3 anos de idade e atividade física na adolescência, mas com associações positivas entre o IMC aos 3, 5 e 6 anos e atividade física moderada e moderada-a-vigorosa na adolescência. Estes resultados aparentemente curiosos podem ter alguma justificação pelo fato de que, contrariamente à aptidão cardiorrespiratória, que é considerada uma capacidade, ou condição, mais estável ao longo do tempo (Ekelund, 2008), e onde se julga que a parte genética explique cerca de 40 a 50% dela (Bouchard et al., 1998; Bouchard et

al., 1986), a atividade física é um comportamento altamente variável, que facilmente se modifica, influenciado por uma complexa interação entre fatores biológicos, sociais, culturais e ambientais (Hallal et al., 2012). Para além disso, existem dados que sugerem que as associações com parâmetros de saúde tendem a ser mais robustas para a aptidão cardiorrespiratória do que para a atividade física (Lee et al., 2011; Salonen et al., 2011).

Tal como no Artigo IV desta tese, Hallal et al. (2006) não encontraram associações entre o IMC no primeiro e quarto anos de vida e os níveis de atividade física, na adolescência. Teria sido interessante esse estudo ter verificado se para as outras idades durante a infância, para além do primeiro e quarto ano, essa tendência se mantém, para confrontar com os nossos resultados; porém, ao contrário do nosso, onde existem dados de IMC em intervalos periódicos desde o nascimento até aos 6 anos, no estudo citado anteriormente (Hallal et al., 2006) apenas foram recolhidos dados antropométricos para as idades previamente referidas.

Conclusões

Esta tese é composta por trabalhos que analisaram detalhadamente os valores de IMC desde o nascimento até aos 6 anos de idade, em intervalos de 6 meses até à idade de 2 anos, e em intervalos de 1 ano desde os 2 até aos 6 anos, como variáveis preditoras de uma série de parâmetros de saúde durante a adolescência, tais como biomarcadores cardiometabólicos, aptidão cardiorrespiratória, tempo sedentário e atividade física. Outros estudos que recorram abordagens semelhantes àquelas utilizadas nos nossos trabalhos seriam de grande interesse para confirmar ou contrapor aos nossos resultados, bem como pesquisas adicionais incidindo sobre outros parâmetros relacionados com a saúde durante a adolescência.

Os nossos resultados reforçam a recomendação da Academia Americana de Pediatria para uma avaliação anual do IMC, como parte de uma estratégia preventiva para crianças e adolescentes (American Academy of Pediatrics, 2017), reconhecendo o potencial valor desta medida de adiposidade na prevenção do excesso de peso e da obesidade desde idades precoces. O

nosso trabalho mostrou que o IMC apresenta desde cedo não só uma forte capacidade discriminatória para identificar uma categoria desfavorável do IMC na adolescência, mas que também o consegue fazer quando são utilizadas outras medidas de adiposidade, tanto em raparigas como em rapazes. Por sua vez, essas medidas de adiposidade também apresentaram habilidade discriminatória para identificar níveis desfavoráveis de alguns biomarcadores inflamatórios e metabólicos em adolescentes.

Também observamos que o excesso de peso ou obesidade (identificados pelo IMC) durante o período pré-escolar foi consistentemente associado a vários parâmetros relacionados com a saúde durante a adolescência, como maior adiposidade, piores indicadores cardiometabólicos e níveis mais reduzidos de aptidão cardiorrespiratória, para ambos os sexos. Por outro lado, não foram observadas associações entre o peso ao nascer e os mesmos parâmetros relacionados com a saúde referidos anteriormente. Tendo em conta os resultados obtidos nas nossas análises, uma detecção precoce de uma condição de excesso de peso através de uma monitorização regular do IMC, e uma consequente intervenção atempada que vise prevenir ou reverter essa condição durante a infância, parece poder contribuir para melhorar uma série de parâmetros de saúde importantes durante a adolescência, além do excesso de peso em si mesmo. O período pré-escolar parece assim ser um período ideal para adotar estratégias consistentes para atingir esses objetivos.

Considerando os nossos objetivos iniciais e as estratégias delineadas para alcançá-los, os resultados obtidos nos artigos originais parecem razoáveis para suportar as seguintes conclusões:

1. O IMC desde idades muito precoces apresentou capacidade discriminatória para corretamente classificar adolescentes numa categoria desfavorável de IMC, percentagem de massa gorda estimada por bioimpedância, perímetro de cintura ou rácio cintura/estatura, em ambos os sexos;
2. Medidas de adiposidade geral (IMC e percentagem de massa gorda) e abdominal (perímetro de cintura, rácio cintura/estatura e rácio

cintura/estatura sentado) apresentaram capacidade para detectar níveis aumentados de alguns biomarcadores inflamatórios e metabólicos em adolescentes, mas nenhuma das medidas de adiposidade prevaleceu sobre as outras;

3. Um IMC desfavorável a partir dos 2 anos de idade foi consistentemente associado a piores perfis inflamatórios e a um aumento da resistência à insulina na adolescência, e a partir dos 5 anos, a um rácio CT/HDL mais elevado na adolescência;

4. O IMC durante os primeiros anos de vida apresentou consistentes associações negativas com a aptidão cardiorrespiratória na adolescência, para ambos os sexos;

5. Em relação à atividade física os resultados obtidos foram mistos, com ausência de associações nas raparigas, e associações positivas entre o IMC aos 3, 5 e 6 anos e atividade física moderada e moderada-a-vigorosa na adolescência, nos rapazes;

6. O peso ao nascer não foi um bom preditor de excesso de peso na adolescência, independentemente da medida de adiposidade utilizada para identificar essa condição;

7. Cumulativamente, o peso ao nascer não apresentou associações com a aptidão cardiorrespiratória, atividade física ou tempo sedentário, nem com qualquer indicador cardiometabólico na adolescência.

CAPÍTULO VI

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